

For Reference

NOT TO BE TAKEN FROM THIS ROOM

For Reference

NOT TO BE TAKEN FROM THIS ROOM

Ex libris
UNIVERSITATIS
ALBERTAENSIS





Digitized by the Internet Archive
in 2020 with funding from
University of Alberta Libraries

<https://archive.org/details/Deshpande1967>

THE UNIVERSITY OF ALBERTA

DEAMINATIVE AND SOLVOLYTIC TRANSFORMATIONS OF SOME

LEVOPIMARIC ACID DERIVATIVES

by



Pandurang D. Deshpande

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN

PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

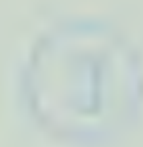
DECEMBER 1, 1967

THE UNIVERSITY OF CHICAGO

DEPARTMENT OF THE HISTORY OF ARTS AND ARCHITECTURE

OFFICE OF THE DEAN

CHICAGO, ILLINOIS



1950

RECEIVED FROM THE UNIVERSITY OF CHICAGO

LIBRARY OF THE UNIVERSITY OF CHICAGO

DEPARTMENT OF THE HISTORY OF ARTS AND ARCHITECTURE

CHICAGO, ILLINOIS

CHICAGO, ILLINOIS

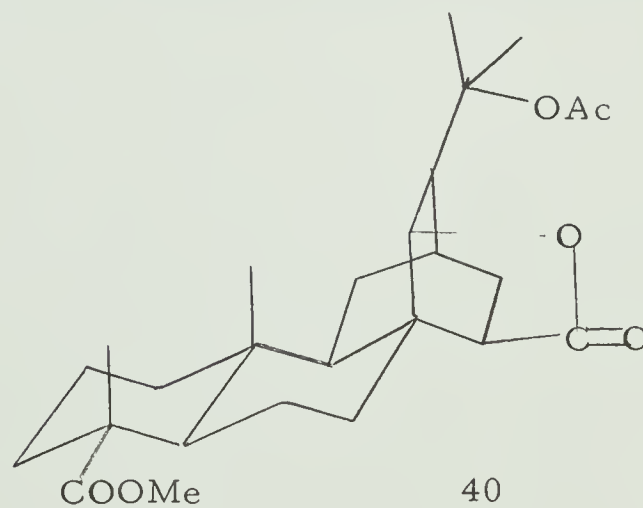
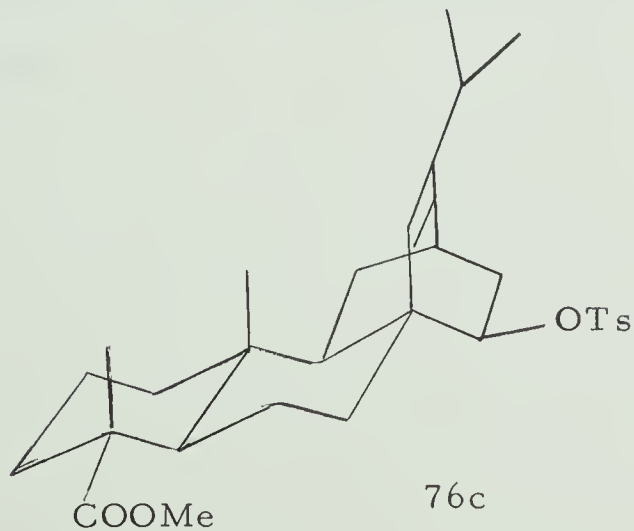
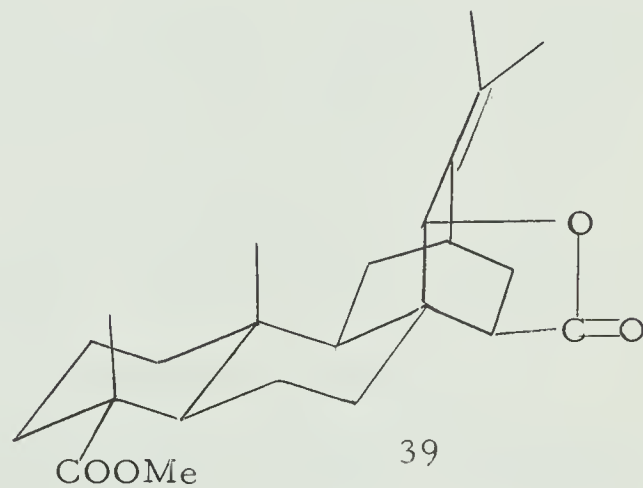
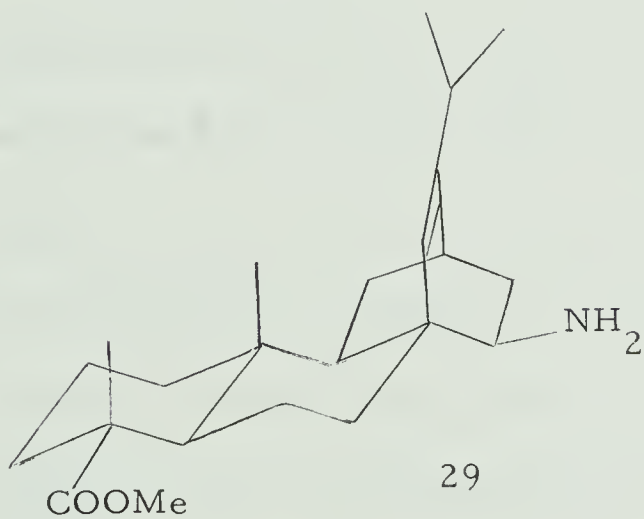
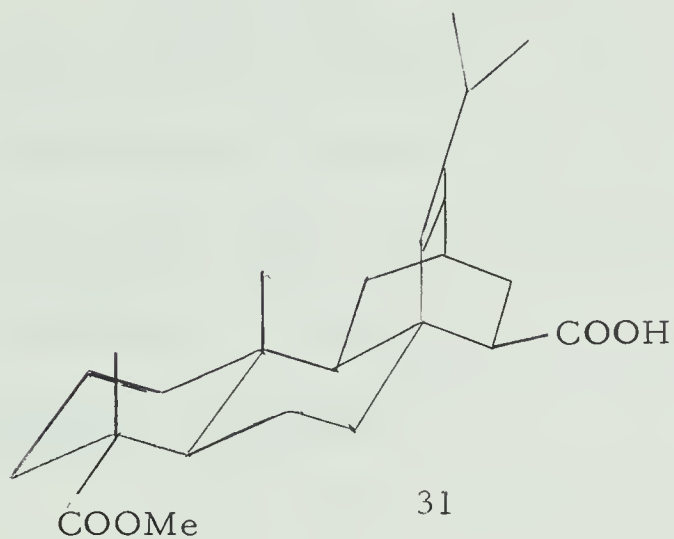
CHICAGO, ILLINOIS

THE UNIVERSITY OF ALBERTA
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read , and recommend
to the Faculty of Graduate Studies for acceptance , a thesis entitled
DEAMINATIVE AND SOLVOLYTIC TRANSFORMATIONS OF SOME
LEVOPIMARIC ACID DERIVATIVES
submitted by Pandurang D. Deshpande , in partial fulfilment of the
requirements for the degree of Doctor of Philosophy.

ABSTRACT

The Diels-Alder adduct (31) of methyl levopimarate and acrylic acid furnishes on oxidation with lead tetraacetate the cyclopropyl lactone 35, the isopropylidene lactone 39 and the acetoxy lactone 40.



The adduct 31 has been transformed into the amine 29 by a reaction sequence involving preparation of the isocyanate 47, reduction of the isocyanate with sodium borohydride and acid hydrolysis of the resulting N-formyl compound 49.

Deamination of amine 29, carried out in aqueous acetic acid, gave a variety of products. Some of these were found to possess a rearranged lycoctonine type partial skeleton containing a bicyclo[3.2.1]octane system while others retained the bicyclo[2.2.2]octane system in the skeleton. Speculation on the mode of formation of the deamination products is included.

Tosylate 76c, prepared from the adduct of levopimaric acid and acetoxyacrylonitrile, has been found to undergo a facile rearrangement from the bicyclo[2.2.2]octane system to a bicyclo[3.2.1]octane system on the surface of silica gel. The rearrangement has also been effected by acetolysis of tosylate 76c. These results indicate that entry into the carbon skeleton of lycoctonine type diterpenoid alkaloids may be made starting from the readily available levopimaric acid.

ACKNOWLEDGEMENT

The author wishes to thank:

Dr. W. A. Ayer for the untiring patience and assistance throughout the course of this project.

The academic and technical staff of the Chemistry Department of the University of Alberta for their cooperation and advice.

The Province of Alberta and the University of Alberta for financial assistance.

Mrs. Gail Conway for typing the manuscript of this thesis.

TABLE OF CONTENTS

	Page
1. Introduction	1
2. The Deamination Approach	20
Experimental	111
3. The Solvolytic Approach	156
Experimental	198
4. Genesis of the Deamination Products	217
Experimental	238
5. Figures	245
6. References	255

LIST OF TABLES

		P a g e
Table I	Mass spectral data for compounds 63-68.	92
Table II	Infrared spectral data for compounds 63-68.	92
Table III	Nuclear magnetic resonance spectral data for compounds 63-68.	93
Table IV	Spin-decoupling experimental data for chlorosulfonamide 68.	98
Table V	Spectral data for dinitro compound 61 and nitroalcohol 73.	105

LIST OF FIGURES

Fig. 1	Nuclear magnetic resonance spectrum of the adduct 31.	245
Fig. 2	Nuclear magnetic resonance spectrum of the isopropenyl lactone 37.	245
Fig. 3	Nuclear magnetic resonance spectrum of the diene acid 38.	245
Fig. 4	Nuclear magnetic resonance spectrum of the isopropylidene lactone 39.	246
Fig. 5	Infrared spectrum of the α, β unsaturated ketone 41 in nujol.	246
Fig. 6	Nuclear magnetic resonance spectrum of the α, β unsaturated ketone 41.	247
Fig. 7	Nuclear magnetic resonance spectrum of the amine 29.	248
Fig. 8	Infrared spectrum of the amine hydrochloride 50 in nujol.	248
Fig. 9	Nuclear magnetic resonance spectrum of the acetate 402 (52).	248
Fig. 10	Infrared spectrum of the ketoolefin 56 in carbon tetrachloride.	249
Fig. 11	Nuclear magnetic resonance spectrum of the ketoolefin 56.	249

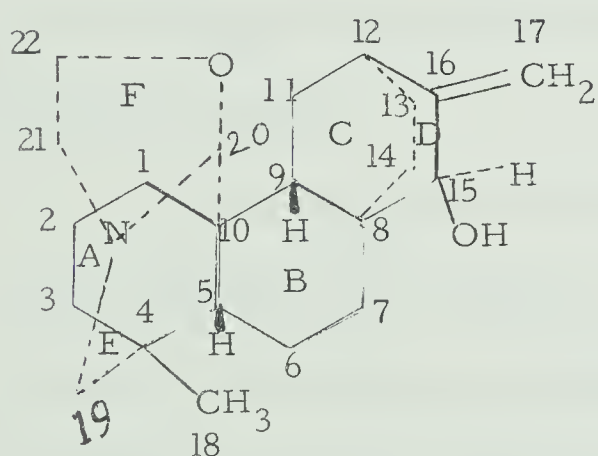
Fig. 12	Nuclear magnetic resonance spectrum of the ketoacetate 376 (55a).	249
Fig. 13	Infrared spectrum of the nitroacetate 400 (57) in chloroform.	250
Fig. 14	Nuclear magnetic resonance spectrum of the nitroacetate 400 (57).	250
Fig. 15	Nuclear magnetic resonance spectrum of compound 62.	250
Fig. 16	Infrared spectrum of the trinitro compound 60 in chloroform.	251
Fig. 17	Infrared spectrum of the dinitro compound 61 in chloroform.	251
Fig. 18	Infrared spectrum of the nitroalcohol 73 in chloroform.	251
Fig. 19	Nuclear magnetic resonance spectrum of the dinitro compound 60.	252
Fig. 20	Nuclear magnetic resonance spectrum of the dinitro compound 61.	252
Fig. 21	Nuclear magnetic resonance spectrum of the nitroalcohol 73.	252
Fig. 22	Nuclear magnetic resonance spectrum of the ketoacid 80a.	253
Fig. 23	Nuclear magnetic resonance spectrum of the <u>endo</u> acetate 76b.	253

Fig. 24	Nuclear magnetic resonance spectrum of the <u>exo</u> acetate 81b.	253
Fig. 25.	Nuclear magnetic resoance spectrum of the adduct 77a.	254
Fig. 26	Infrared spectrum of the diene 82a in chloroform.	254
Fig. 27	Nuclear mangetic resonance spectrum of the diene 82a.	254

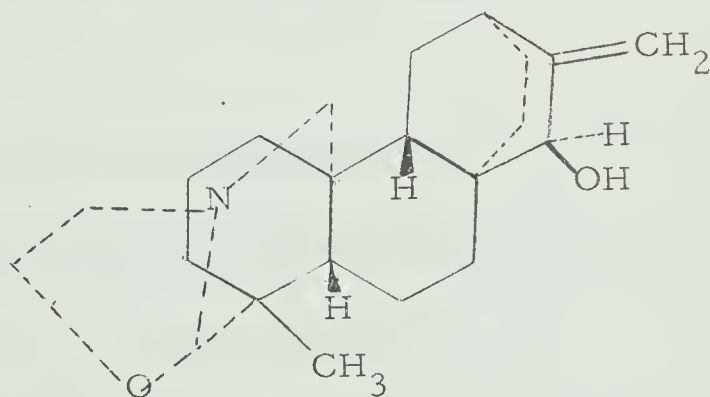
1. INTRODUCTION

The aconite alkaloids constitute a class of bases which occur in the *Aconitum*, *Delphinium* (family Ranunculaceae) and *Garrya* (family Cornaceae) genera of plants. Several reviews¹⁻³ pertaining to the chemistry of these nitrogen containing diterpenoid compounds have appeared during the past few years. They can be broadly divided into three classes: (a) the Atisine class; (b) the Hetisine class; (c) the Lycoctonine class.

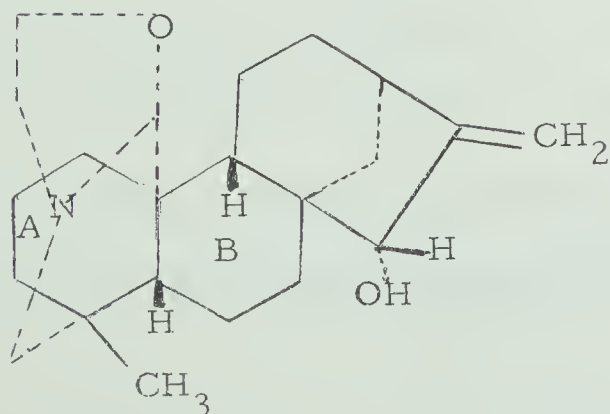
Atisine (1), isoatisine (2), veatchine (3) and garryine (4) may be taken as representative members of class (a). They have a C-20



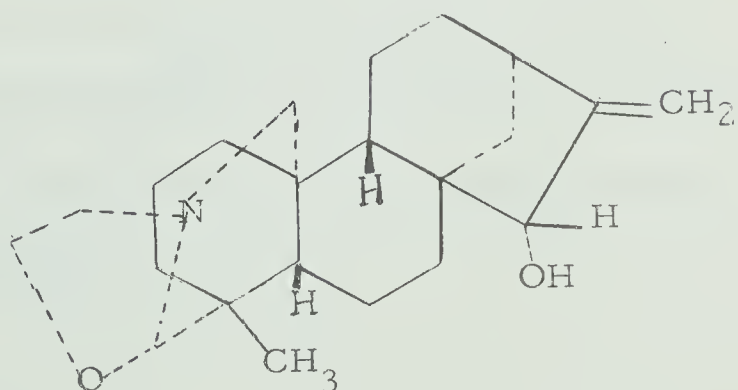
1



2



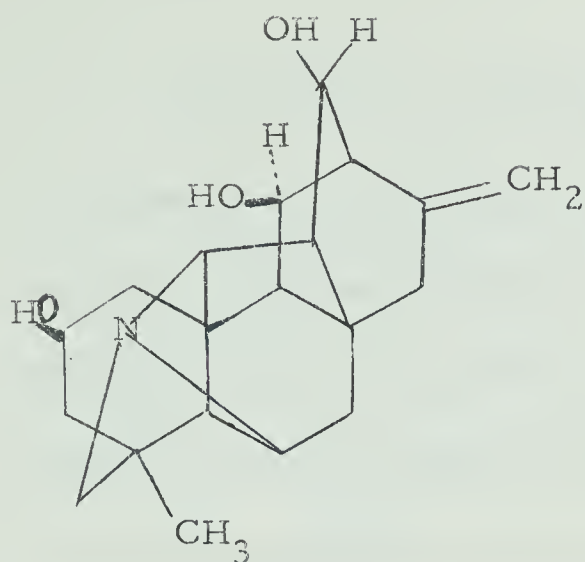
3



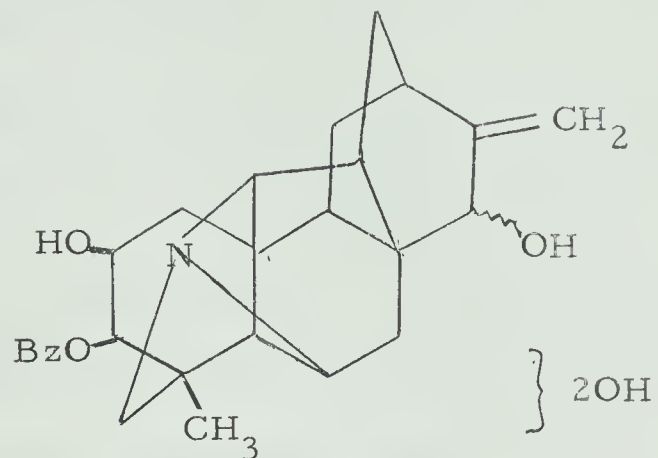
4

carbon skeleton indicative of their diterpenoid nature. A distinction among these can be made on the basis of the presence of a bicyclo [2·2·2]octane system in the compounds represented by atisine and isoatisine, and a bicyclo [3·2·1]octane system in veatchine and garryine. Closure of the oxazolidine ring at C-19 constitutes the iso- series. Some members of the atisine class do not possess a closed ring with N and O as heteroatoms. These penta- or hexacyclic compounds are nontoxic, possess few substituents, and afford on dehydrogenation aromatic compounds which are substituted phenanthrenes or azaphenanthrenes. The structures of these representatives, as indicated in diagrams 1-4, have been arrived at after a thorough chemical investigation and have been confirmed by partial or total syntheses⁴ by different groups of workers.

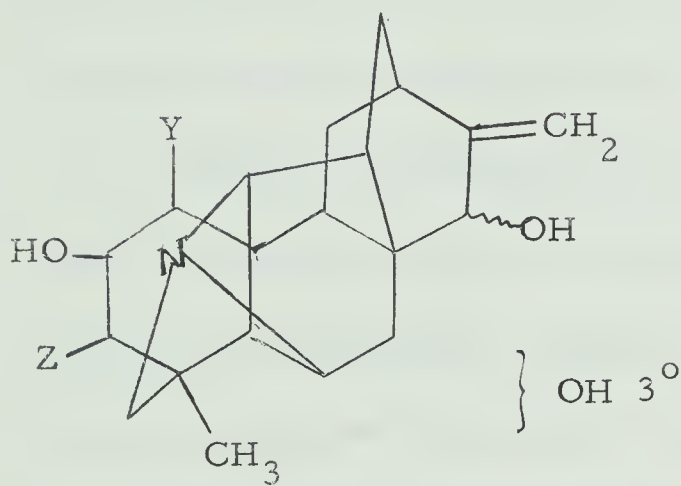
The Hetisine class shows an interesting structural feature which clearly marks it as a different class from the one discussed above although the skeletons are similar. This consists in the alkylation of nitrogen by a carbon of ring B and an additional carbon-carbon bond. Although Wiesner¹ proposed the correct skeleton for hetisine on the basis of chemical degradation, the location of substituents as shown in 5 was established by an X-ray crystallographic examination by Przybylska⁵. Ignavine (6), hypognavine (7) and kobusine (8) are other examples which exhibit hetisine type structural features.



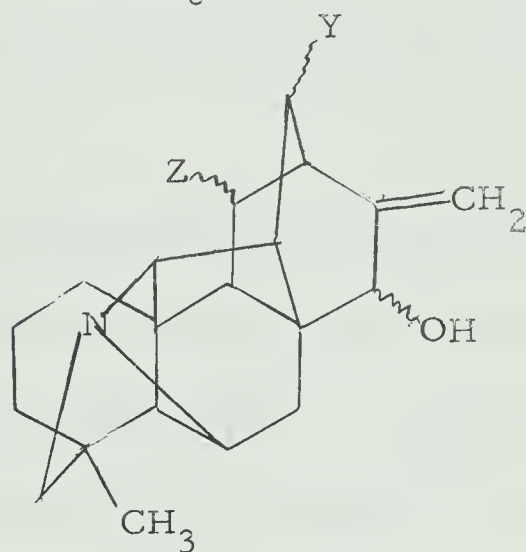
5



6



7



8

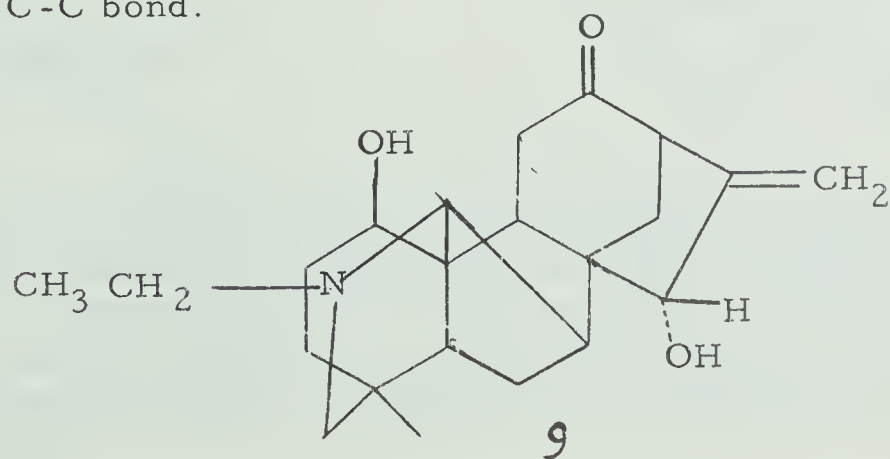
Y = H, Z = OBz

or Y = OBz, Z = H

Y = H, Z = OH

or Y = OH, Z = H

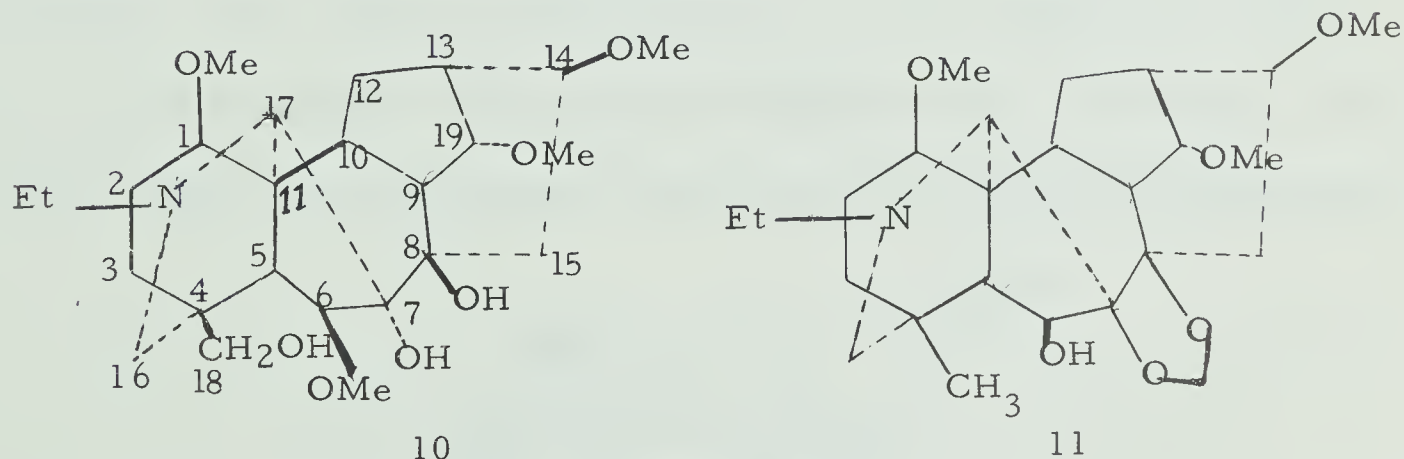
The alkaloid songorine (9), although it does not strictly belong to this class, shows a similarity with the hetisine type bases in possessing the additional C-C bond.



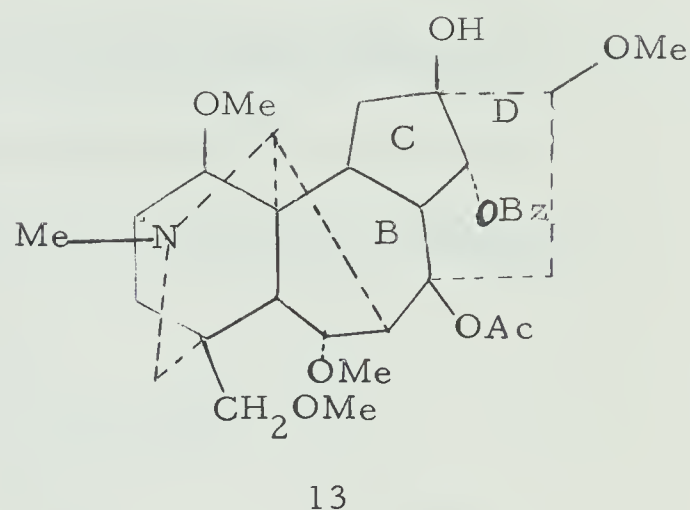
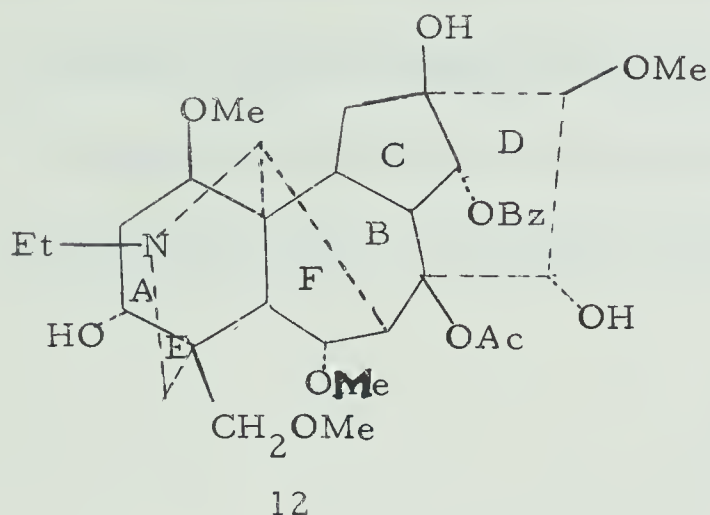
9

The third type of diterpenoid alkaloids, which will be referred to as the Lycoctonine class, differs from the other types in several respects. Bases belonging to this class are highly oxygenated, toxic substances having C_{19} rather than C_{20} skeletons. Another important feature which distinguishes them from the other types is the presence of a seven membered ring attached to a bicyclo[3.2.1]octane system. Salient features of the chemistry of important members of this class have been summarized by Marion⁶.

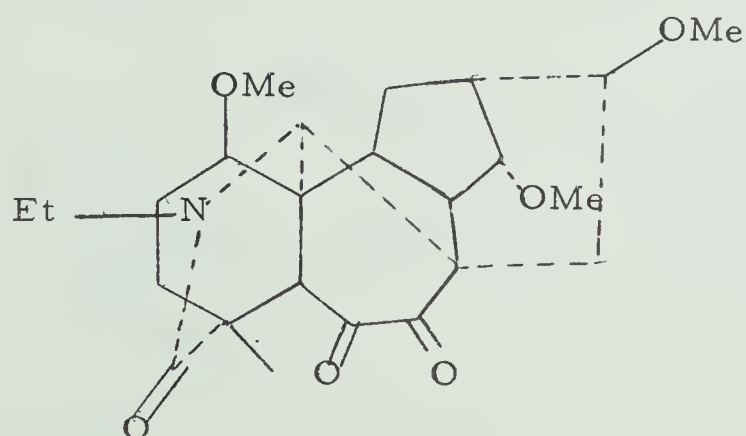
Further classification into two groups based on the orientation of the C-6 oxygen function, which apparently plays a significant role in neutral permanganate oxidation*, has been made⁷. Lycoctonine (10), delpheline (11) and others which have the C-6 oxygen function β -oriented constitute one group, while aconitine (12) and delphinine (13), possessing this function with an α -orientation, form the other.



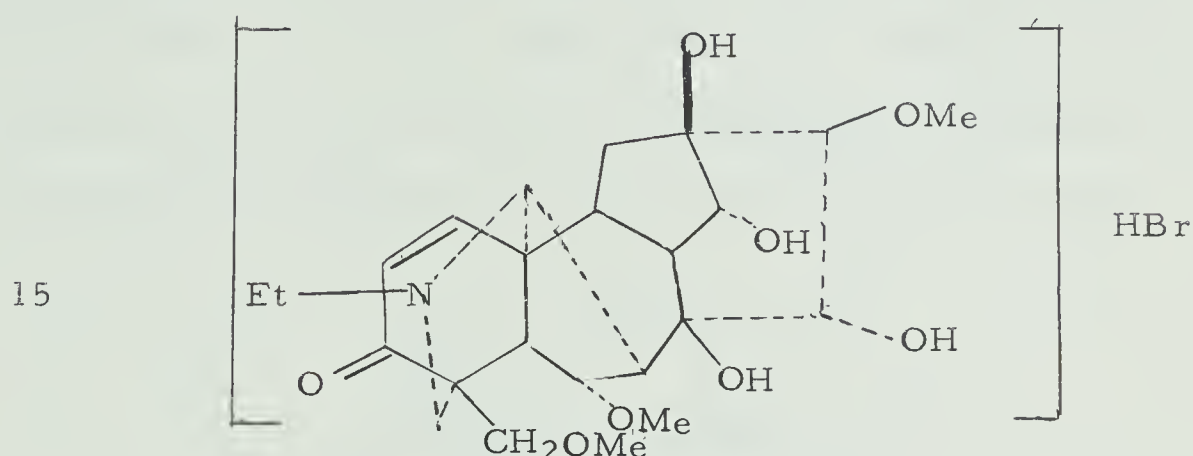
* Aconitine and delphinine form secondary bases by loss of the N-alkyl chain. Lycoctonine and delpheline give rise to lactams by oxidation of the C-16 methylene group. This difference is attributed to steric hindrance caused by the C₆ α -methoxy or hydroxy groups in aconitine type bases which results in oxidation of the methylene group in the N-alkyl chain.



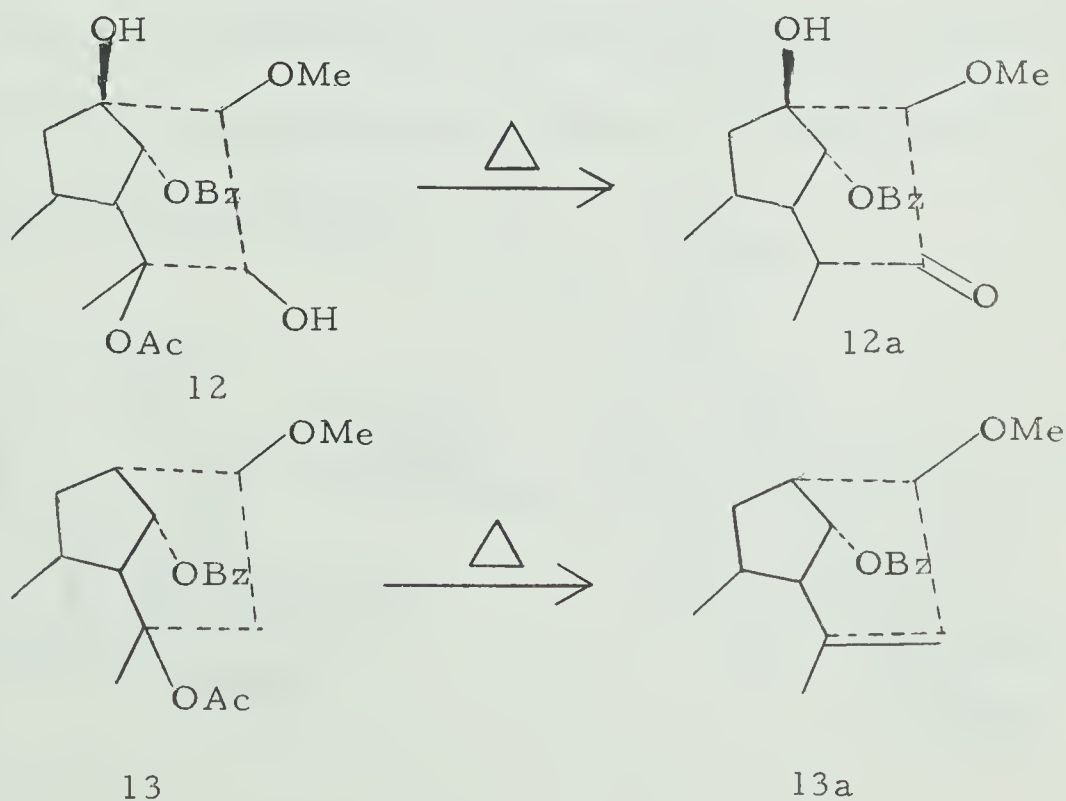
Lycoctonine (10), which occurs in both the *Aconitum* and *Delphinium* species of plants, either as such or as monoester amide or imide (formed with acetic acid, succinic acid or methyl succinic acid and anthranilic acid) was the first member in this class whose structure was rigorously established by chemical and X-ray methods⁸. Furthermore, its absolute stereochemistry was established by Przybylska and Marion from more refined X-ray investigation^{8b}. This made lycoctonine a useful reference compound and correlation of an unknown structure with a derivative of lycoctonine has been useful as a tool in structural elucidation. The alkaloid delpheline (11), for instance, was transformed into the diketone 14 which was also obtained from lycocton-



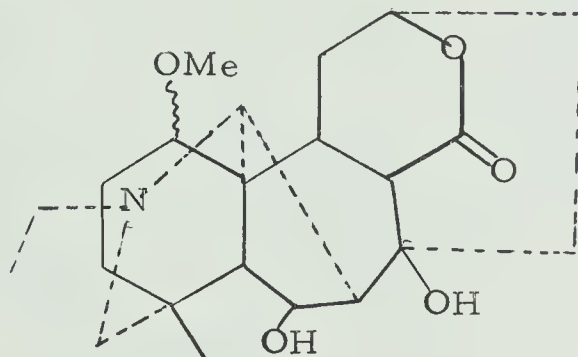
ine⁶. The presence of the lycoctonine type skeleton in aconitine (12), originally inferred from the results of its chemical degradation, was corroborated by X-ray crystallographic examination⁹ of aconinone hydrobromide (15). This latter substance was obtained by oxidation of



the alcoholic function in ring A of aconitine to a ketone followed by elimination of methanol. Besides the difference shown in neutral permanganate oxidation, aconitine and delphinine differ from lycoctonine in their ability to undergo a pyrolytic reaction⁶ which results in the formation of pyro derivatives as illustrated by partial structures 12a and 13a

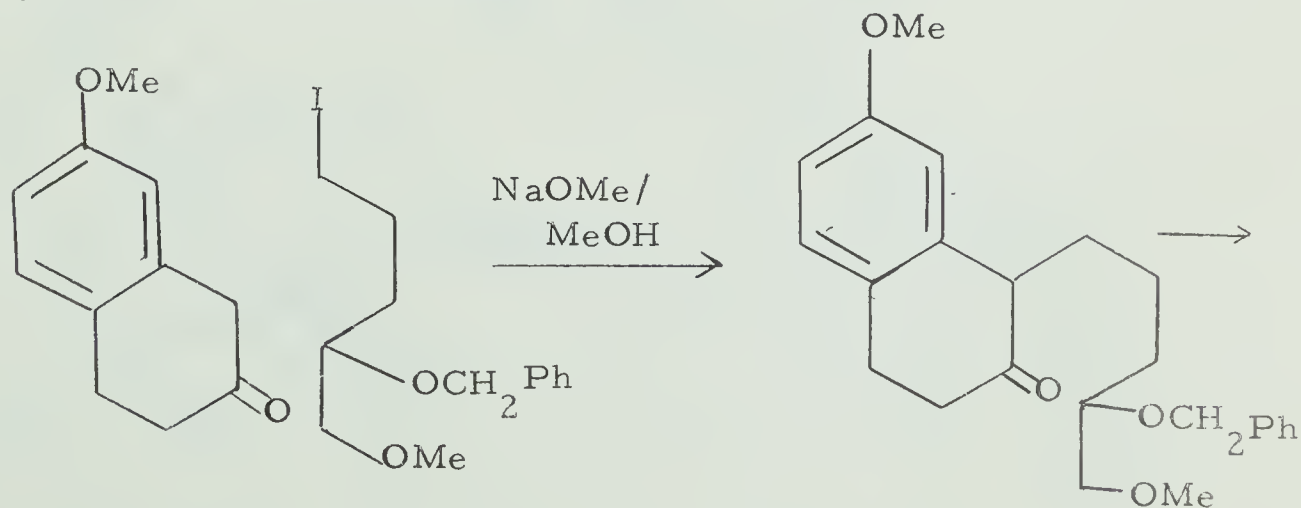


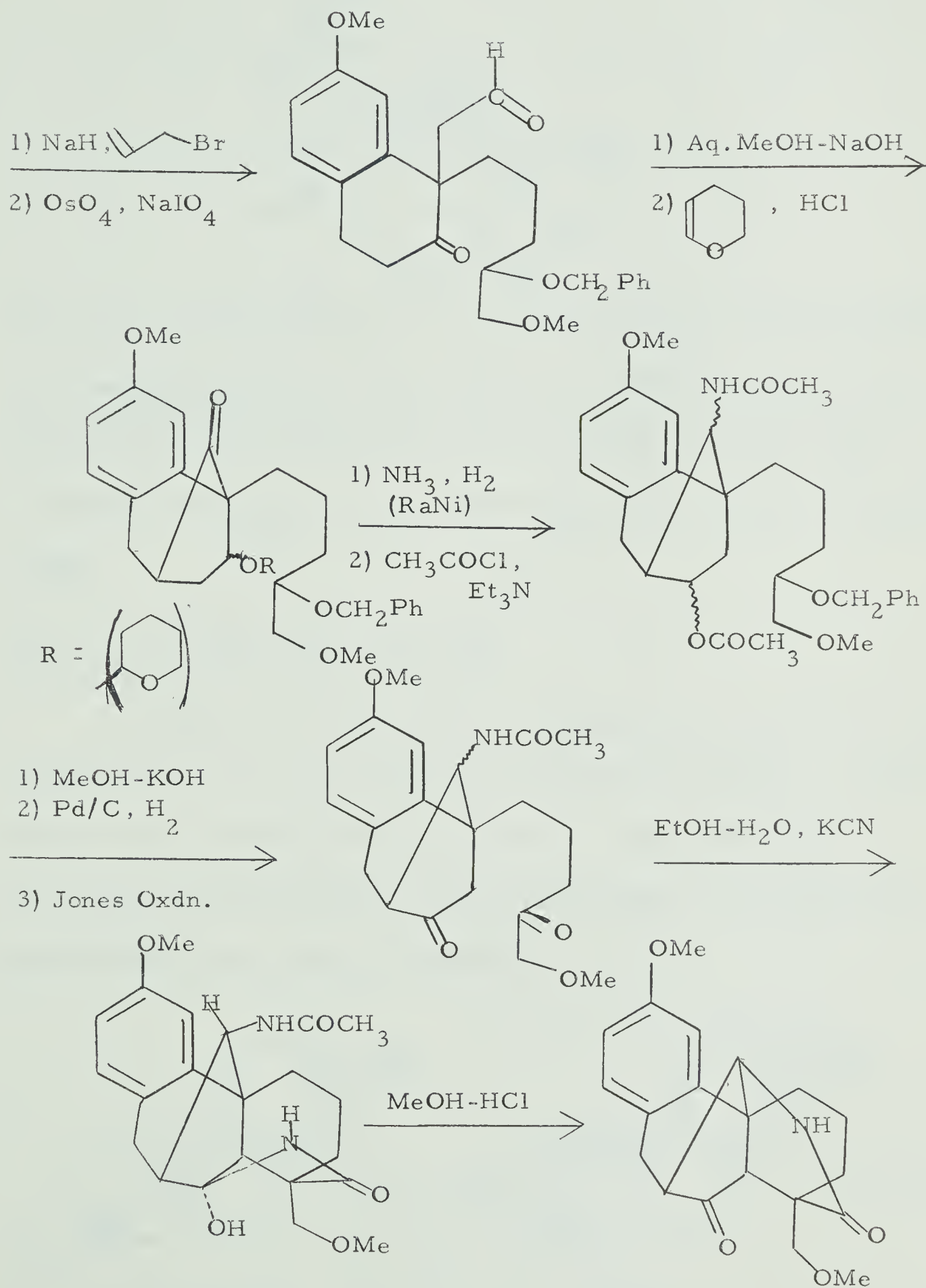
from aconitine (12) and delphinine (13) respectively. Lycoctonine does not form such a pyro derivative. Several other members of the lycoctonine class have been isolated and characterized during recent years by groups led by Marion, Wiesner, Pelletier etc. and investigations are still continuing. An interesting example deserving mention is provided by heteratisine (16) which has been investigated by Pelletier¹⁰ and is the only diterpene alkaloid reported containing a lactone ring.

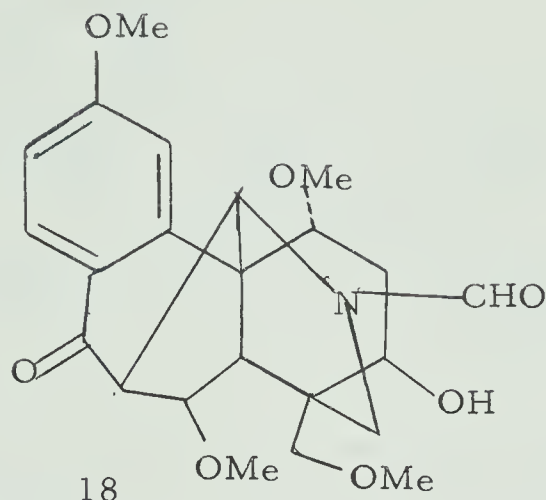


16

In contrast to the extensive synthetic work done in the area of atisine type alkaloids few attempts¹¹ towards partial or total synthesis of the more complex lycoctonine type compounds have been reported. The compound 17 has been synthesized by Wiesner^{11b} starting from methoxytetralone as outlined below.



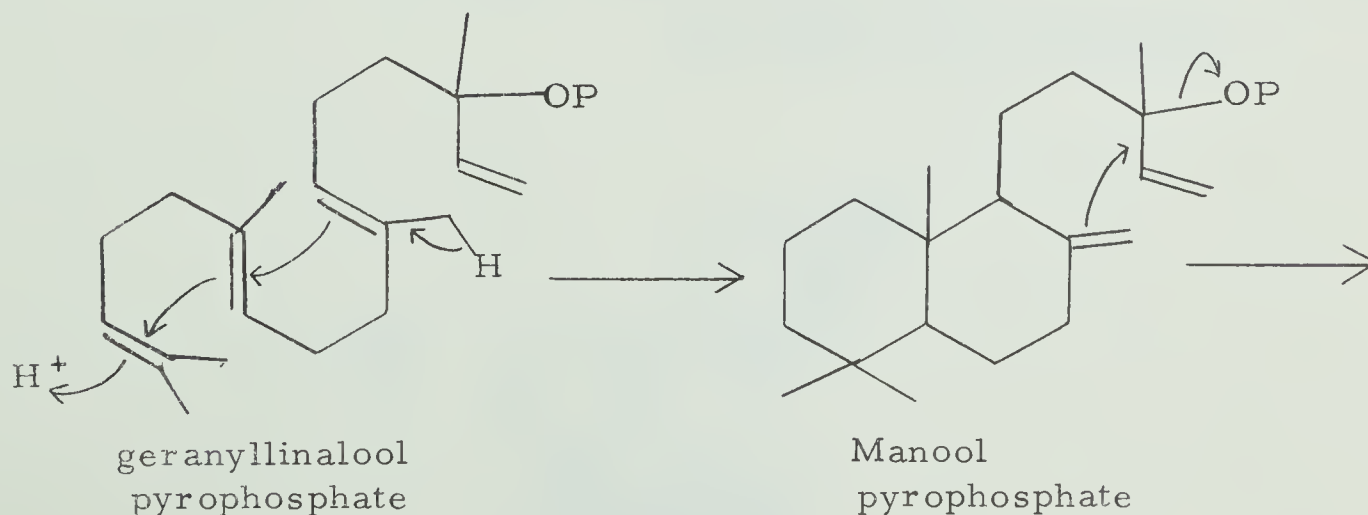


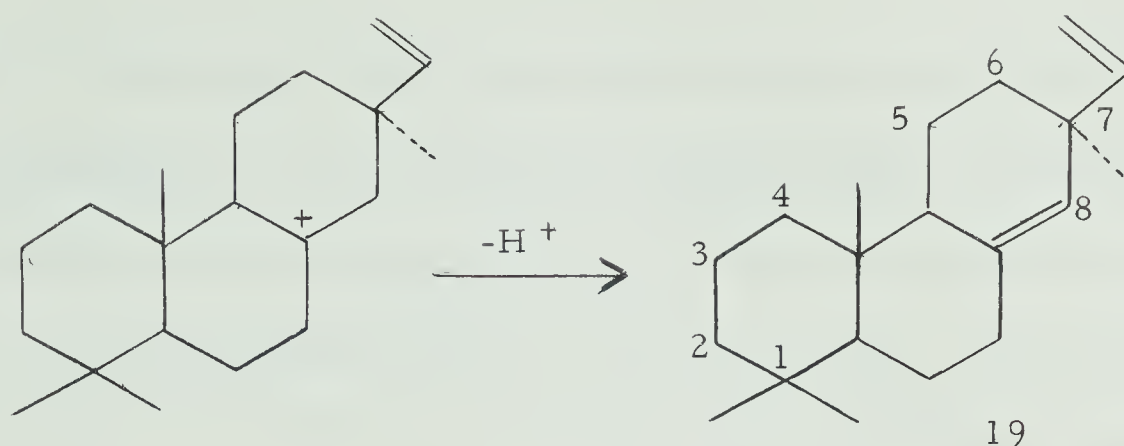


The purpose of the synthesis of 17 appears to be its eventual correlation with compound 18 which is obtained from aconitine (12) by chemical degradation¹² involving extensive rearrangement in rings C and D. Compound 18 could serve as a natural relay in the synthesis of aconitine itself.

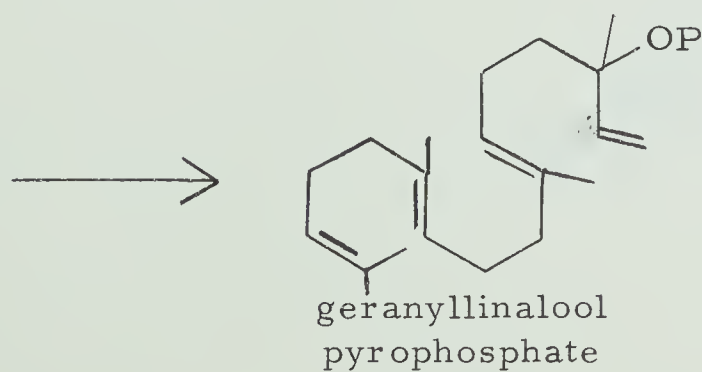
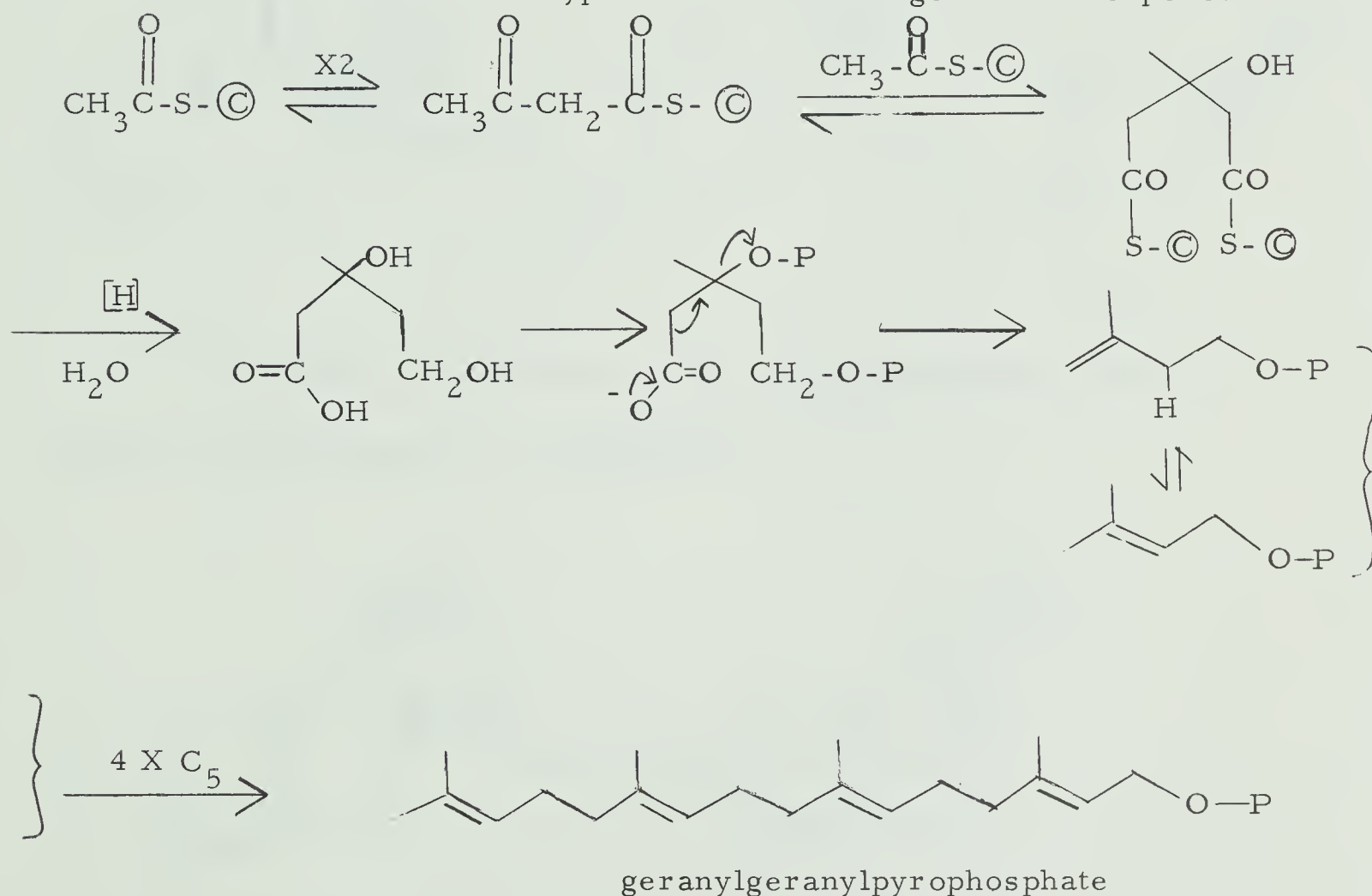
Biosynthesis of Diterpene Alkaloids.

An ingenious scheme has been postulated by Wenkert¹³ for the biogenesis of tetracyclic diterpenes and diterpene alkaloids. Pimaradienes of the type indicated by structure 19, which result from the cyclization of geranyllinalool via geranylgeraneol, are visualized as precursors to this group of compounds.

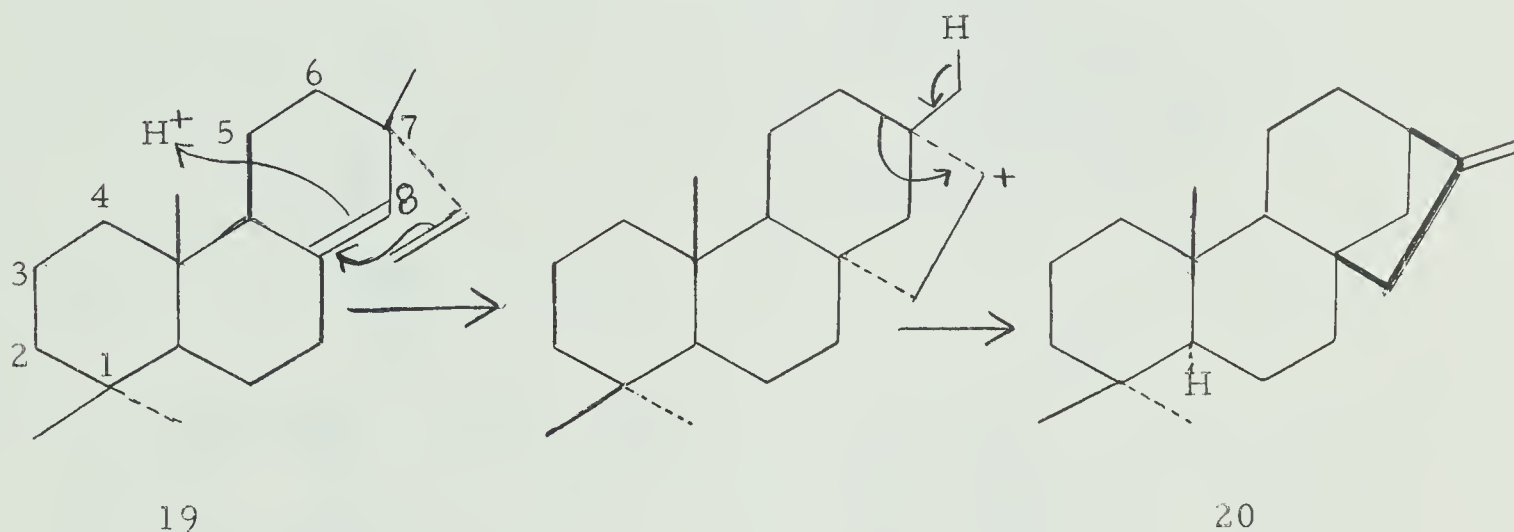




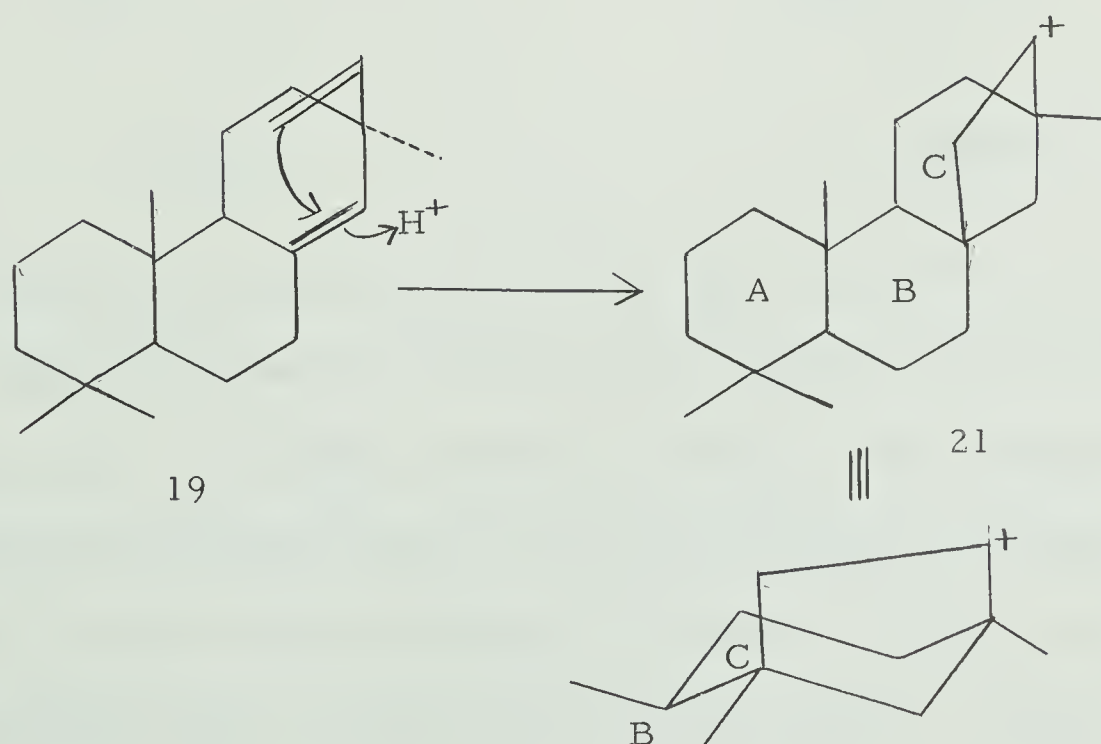
Geranylgeraneol is derived from a mevalonic acid derivative in accordance with the acetate-mevalonate hypothesis for the biogenesis of terpenes¹⁴.

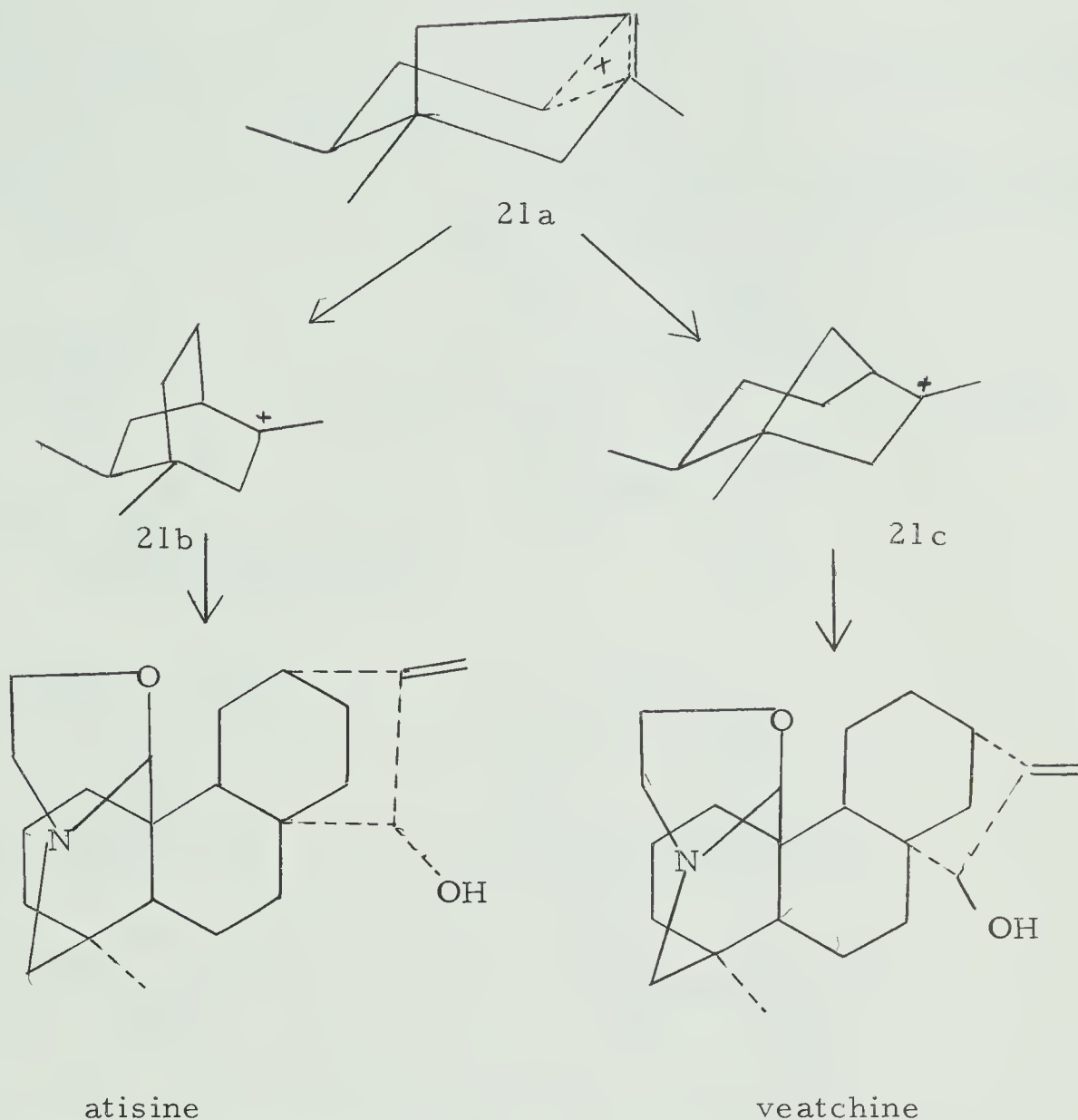


Isolation of this acyclic diterpene alcohol has been reported by S. Dev¹⁵. The pimaradiene 19 may have the C-7 vinyl group β as indicated, or α , and depending on the orientation may give rise to the atisine-garryine type or the phyllocladene (20) type C/D ring junction. The cyclization is presumed to be initiated by protonation of the Δ^8 double bond in 19.



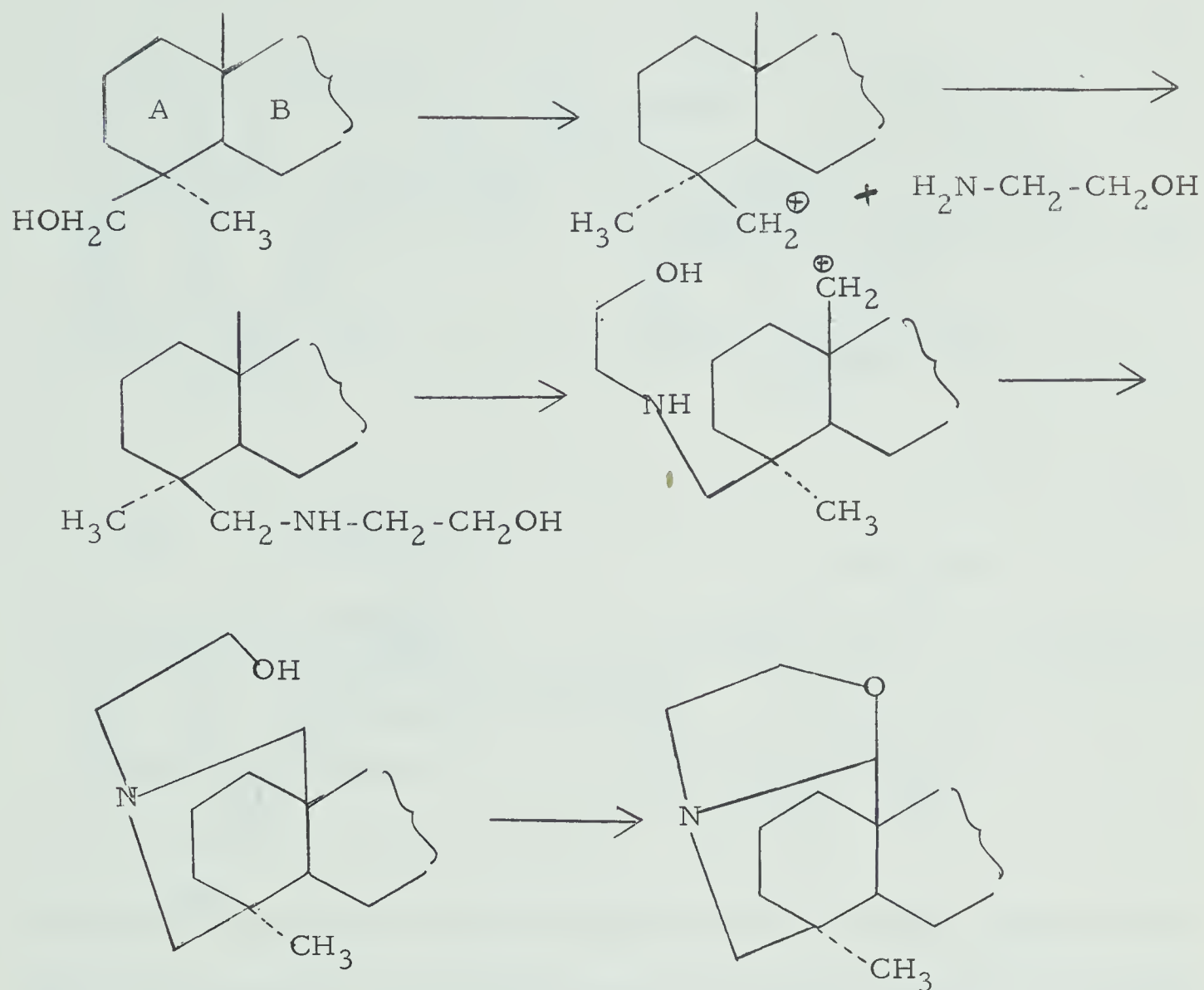
The scheme proposed for the pimaradiene-diterpene alkaloid skeleton transformation is outlined below.



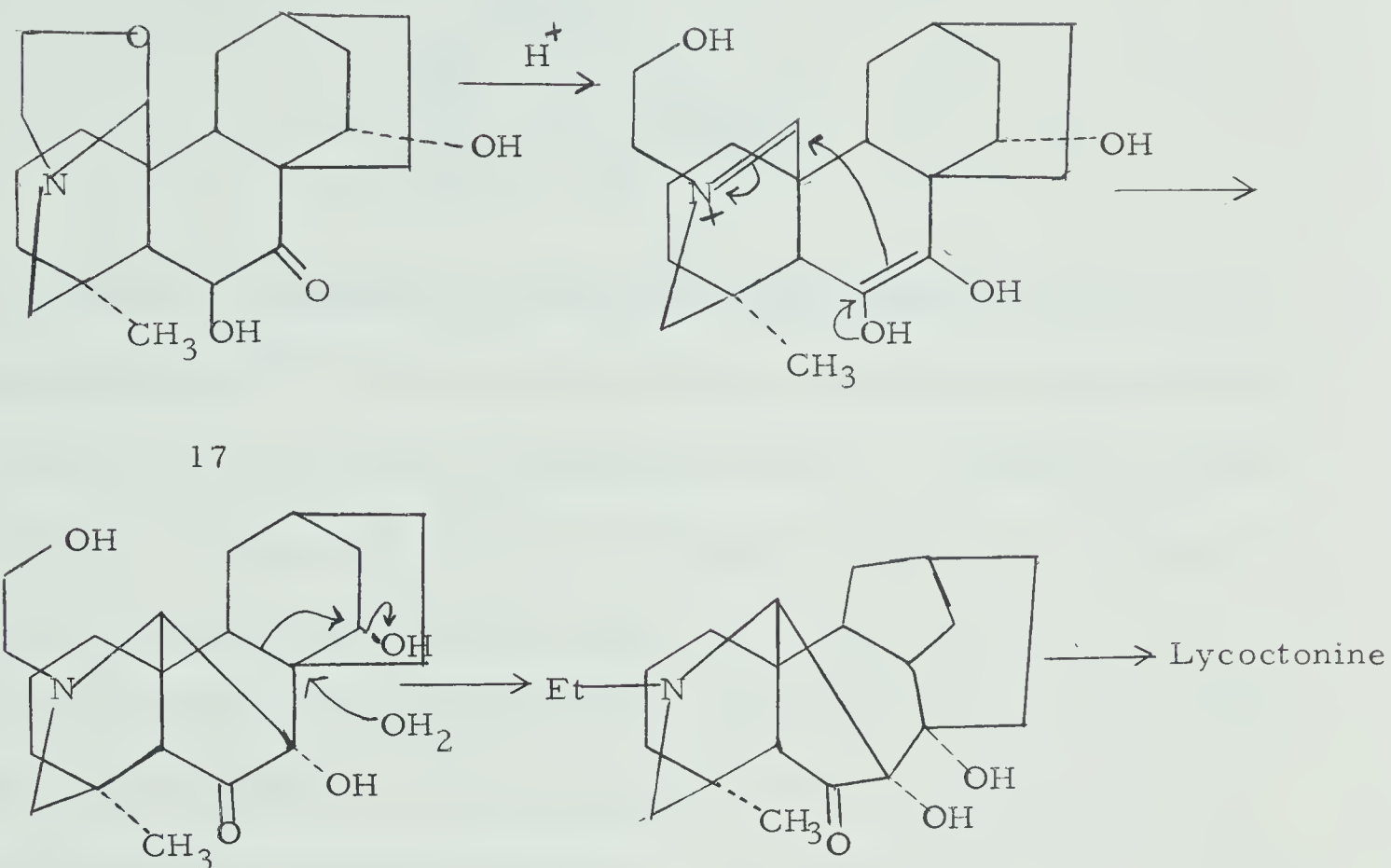


The nonclassical carbonium ion 21a can give rise to the ions 21b and 21c leading to the carbon skeletons of the alkaloids atisine and veatchine, respectively. It should be noted here that the actual configuration of these alkaloids is antipodal¹⁶ to the one depicted in the above scheme. It is not certain whether the biogenetic formation of rings E and F in atisine (1) precedes or follows the C/D ring closure. Whalley¹⁷ has postulated the following scheme for this part of the alkaloid biogenesis.

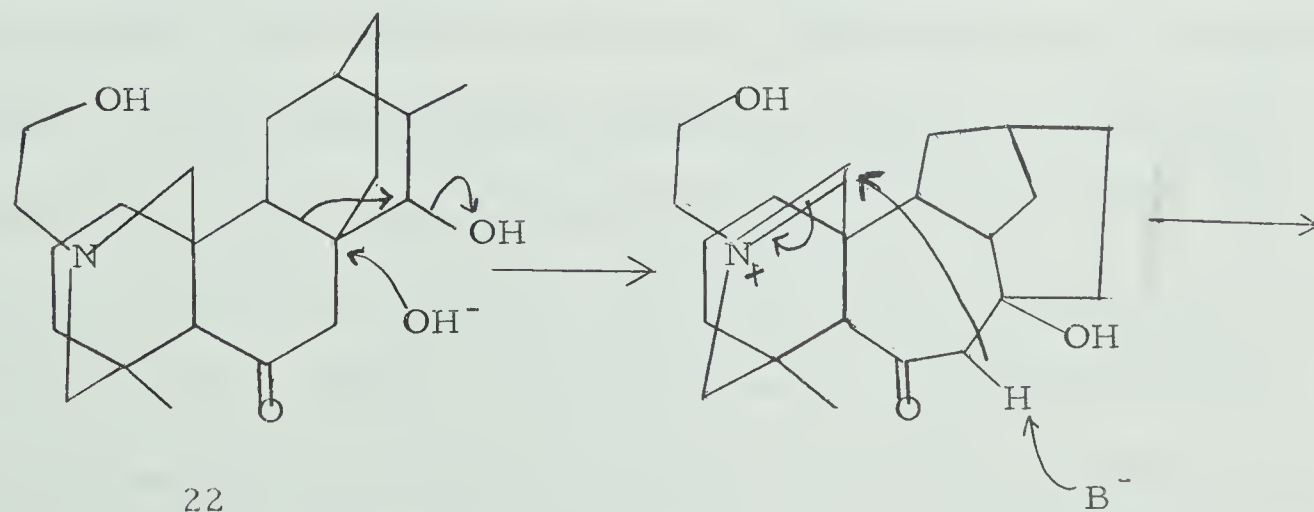


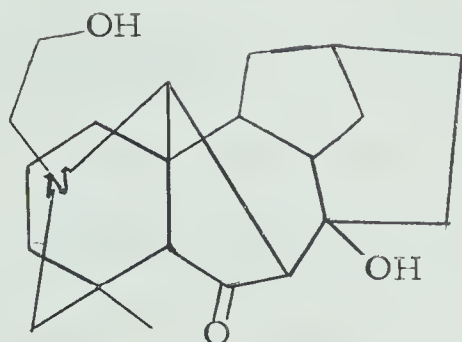


The lycoctonine type alkaloids are considered to be derived from the atisine type. Cookson^{18a} in 1956, suggested that the lycoctonine type skeleton might arise from the skeleton of atisine or its stereoisomer by loss of a methyl group or its equivalent, Wagner-Meerwein rearrangement and cyclization by a Mannich condensation such as shown in the following scheme.



Wiesner^{18b} proposed a similar scheme in which it was suggested that the intermediate 22, easily derivable from atisine, might be demethylated and rearranged to structure 22a as illustrated.





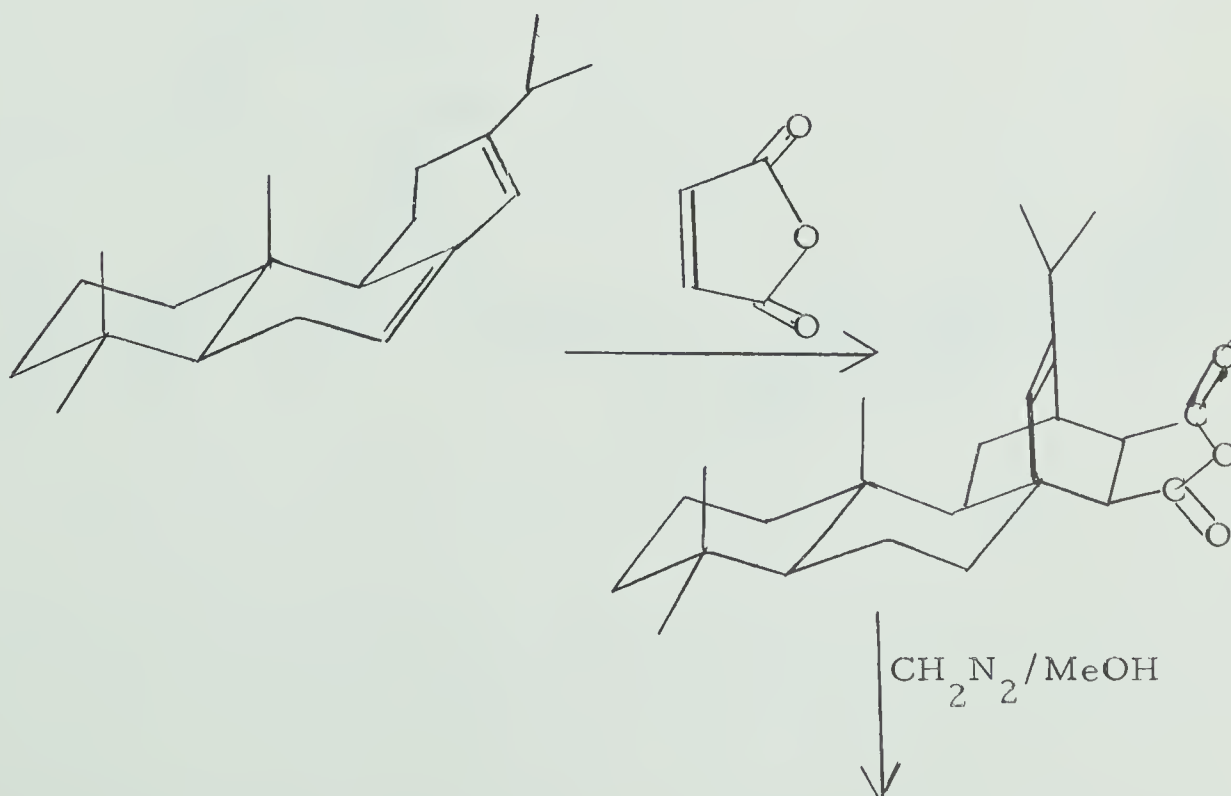
22a

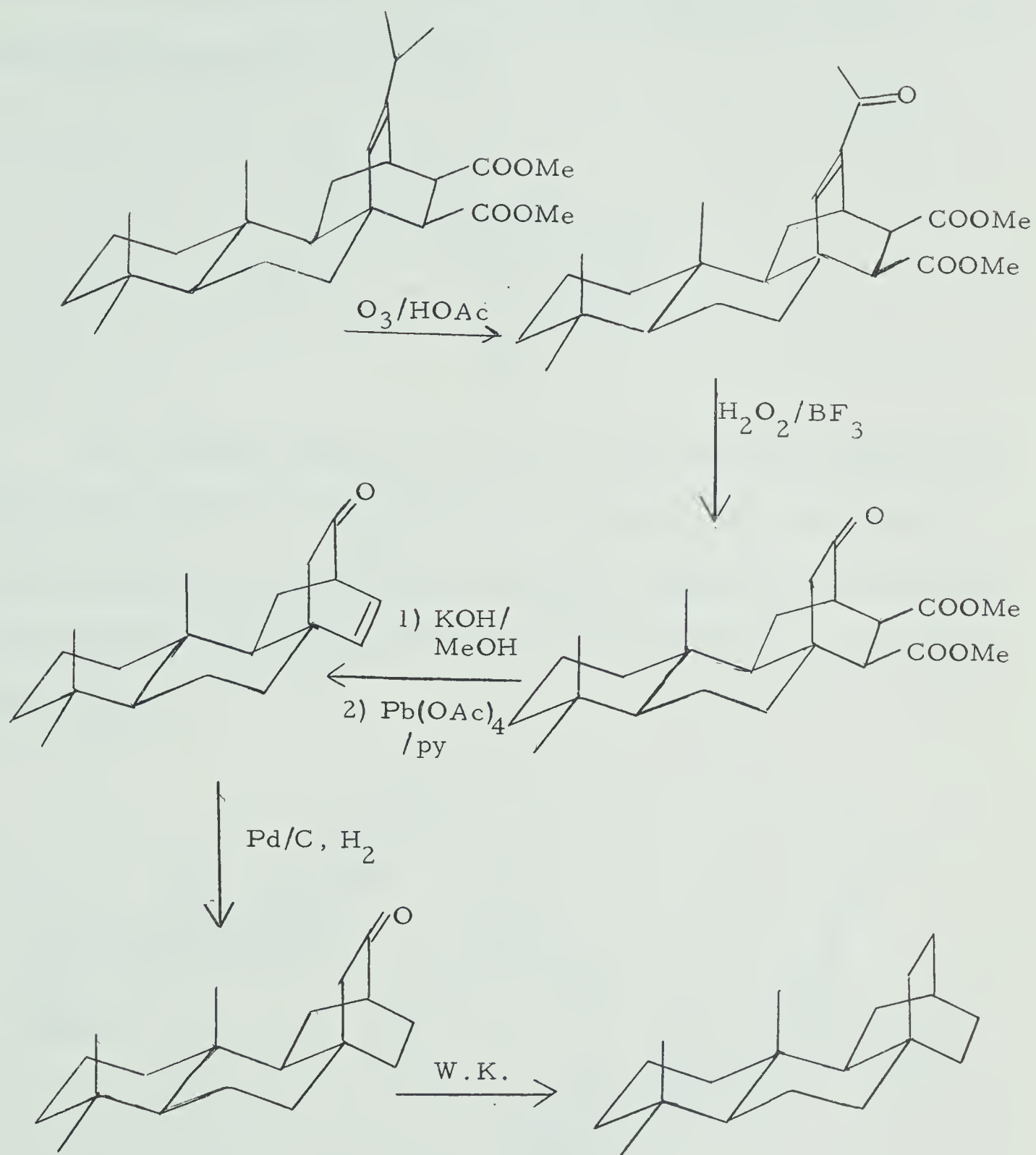
In an attempt to establish the diterpenoid origin of the lycoctonine type alkaloids, Kirby^{19a} carried out experiments involving feeding of labelled mevalonate to young plants of *Delphinium elatum*. Delpheline isolated from these experiments showed no detectable radioactivity, although sterols obtained from the same experiments were found to be active. This lack of activity in delpheline was explained as due to utilization of labelled mevalonate in the formation of non-basic terpenoids before it reached the site of alkaloid synthesis. However, Benn^{19b} has reported isolation of active browniine and lycoctonine from plants of *D. brownii* which were fed with dibenzylethylenediamine mevalonate 2-C¹⁴. This fact lends support to the diterpenoid origin of the lycoctonine type alkaloids. An important feature of the atisine type bases (those with the bicyclo[2.2.2]octane system) is the 15- β configuration of the hydroxyl group. No alkaloids with such a skeleton having an α -oriented C-15 hydroxyl group have been isolated from natural sources, while in the Garrya series (which possess a bicyclo[3.2.1]octane system) they are known to occur. Whalley¹⁷ has suggested that the atisine structure survives because it has the β configuration of the C-15 hydroxyl group,

which is stereochemically not well set up for rearrangement with participation of the C_8-C_9 bond (structure 1). It is possible, therefore, that with an Δ -oriented C-15 hydroxyl group or its equivalent, rearrangement to the lycoctonine skeleton is extremely facile in nature.

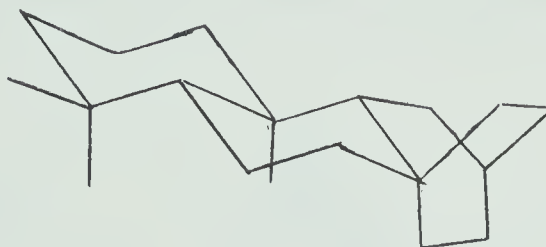
It occurred to us that such a hypothesis could be tested in the laboratory on an appropriately functionalized system derived from levopimaric acid, a diterpenoid compound of known structure and configuration. Furthermore if this plan succeeded it would provide a general method for entry into the carbon skeleton of the diterpene alkaloids with the rearranged lycoctonine skeleton.

The atisine skeleton itself has been constructed starting from abietic acid derivatives by two groups^{16, 20}. The scheme¹⁶ utilized in this synthesis is shown below.



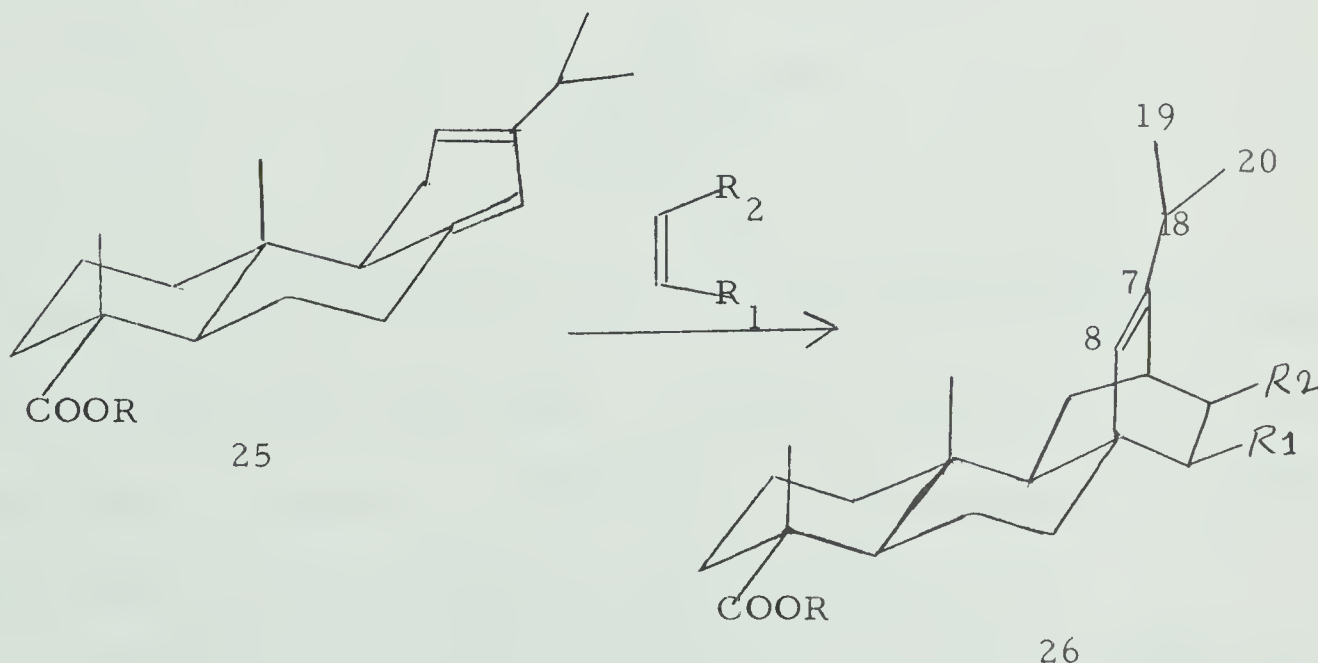


The C-19 hydrocarbon 23 was shown to be the antipode of compound 24 obtained by degradation of atisine.



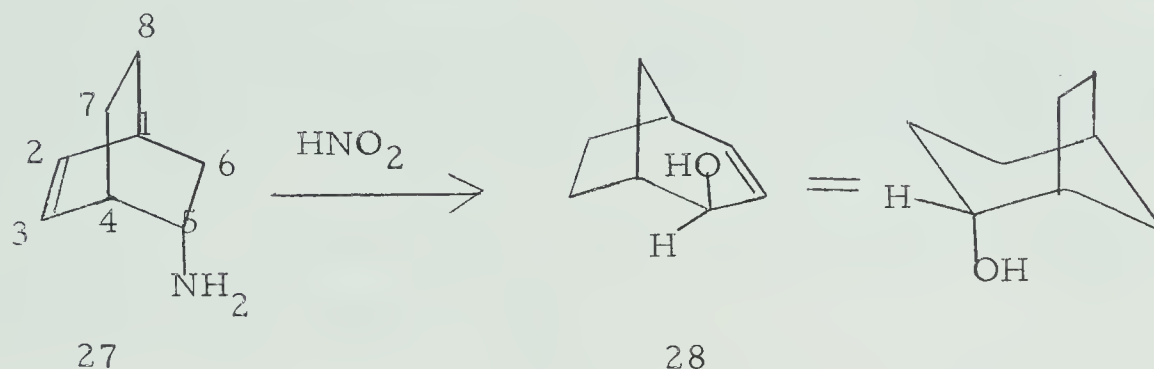
24

Our problem therefore consisted in first making an appropriate Diels-Alder adduct 26 from levopimaric acid (25) ($R = H$) such that the function R_1 (coming from the dienophile) could be transformed into a suitable leaving group and then in investigating the rearrangement of this system.

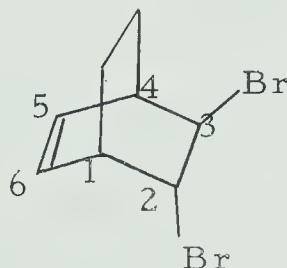


An example which illustrates the desired rearrangement was provided by the work of Wildman and Saunders^{21a} and later in a more elaborate way by Goering, Greiner and Sloan^{21b}. These workers have shown

that deamination of endo 5-amino bicyclo[2.2.2]oct-2-ene (27) in aqueous acetic acid or in glacial acetic acid gives a rearrangement product to which they assigned the structure and stereochemistry as shown in 28.



This indicates that the saturated carbon C-7 in 27 migrates in preference to the vinylic group. It is also known²² that in the solvolysis of the trans dibromide (i) the saturated carbon preferentially migrates

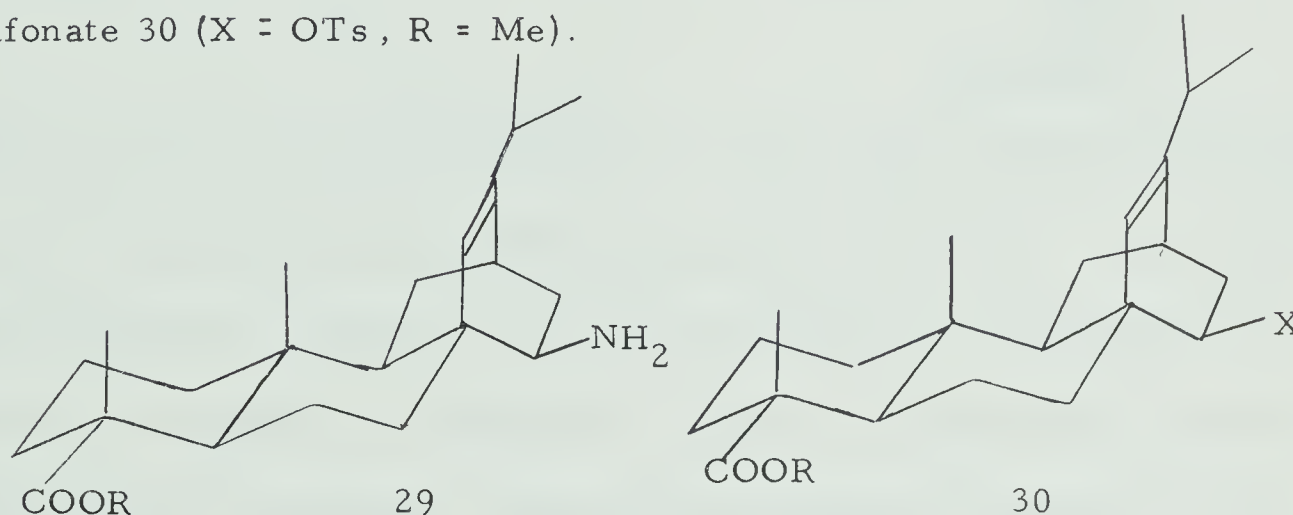


in spite of the fact that the bromine on carbon 3 is favorably situated for migration of the vinyl group. Goering^{21b} has shown that in the solvolysis of tosylates corresponding to the above endo-5-aminobicyclo[2.2.2]oct-2-ene the product formed is analogous to 28.

With these ideas in the background we set out to construct the partial skeleton of the rearranged diterpene alkaloids. The following pages report the results, sometimes unexpected, of the investigation of this problem.

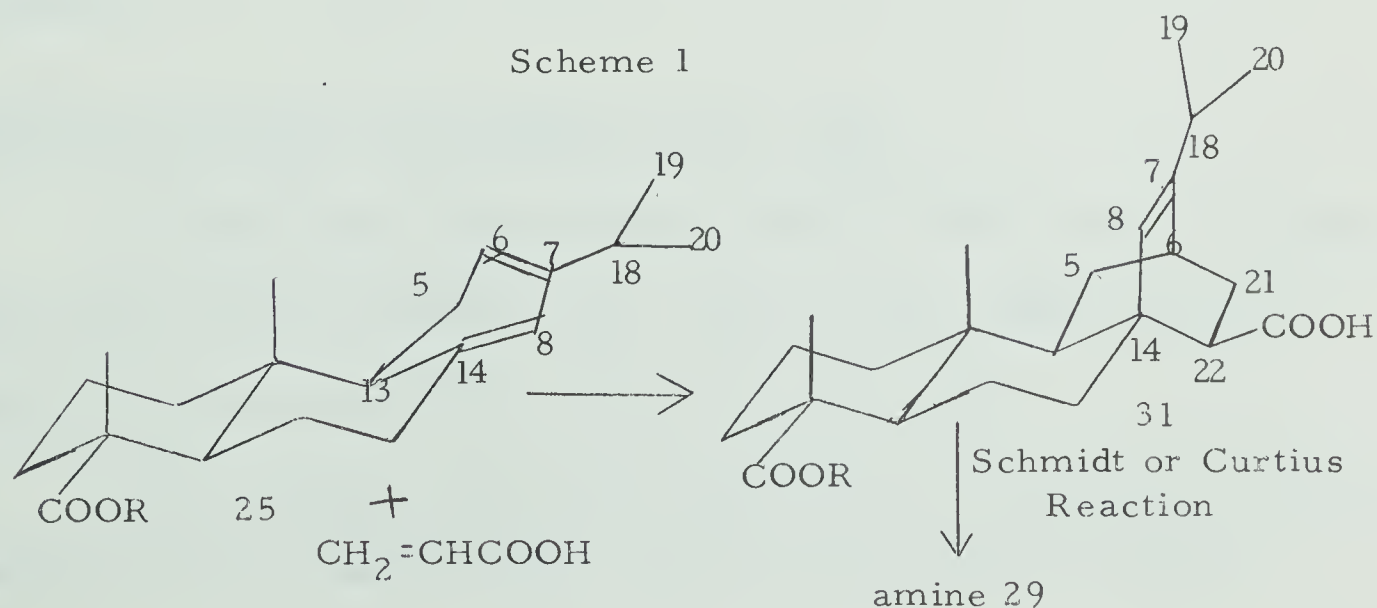
2. THE DEAMINATION APPROACH

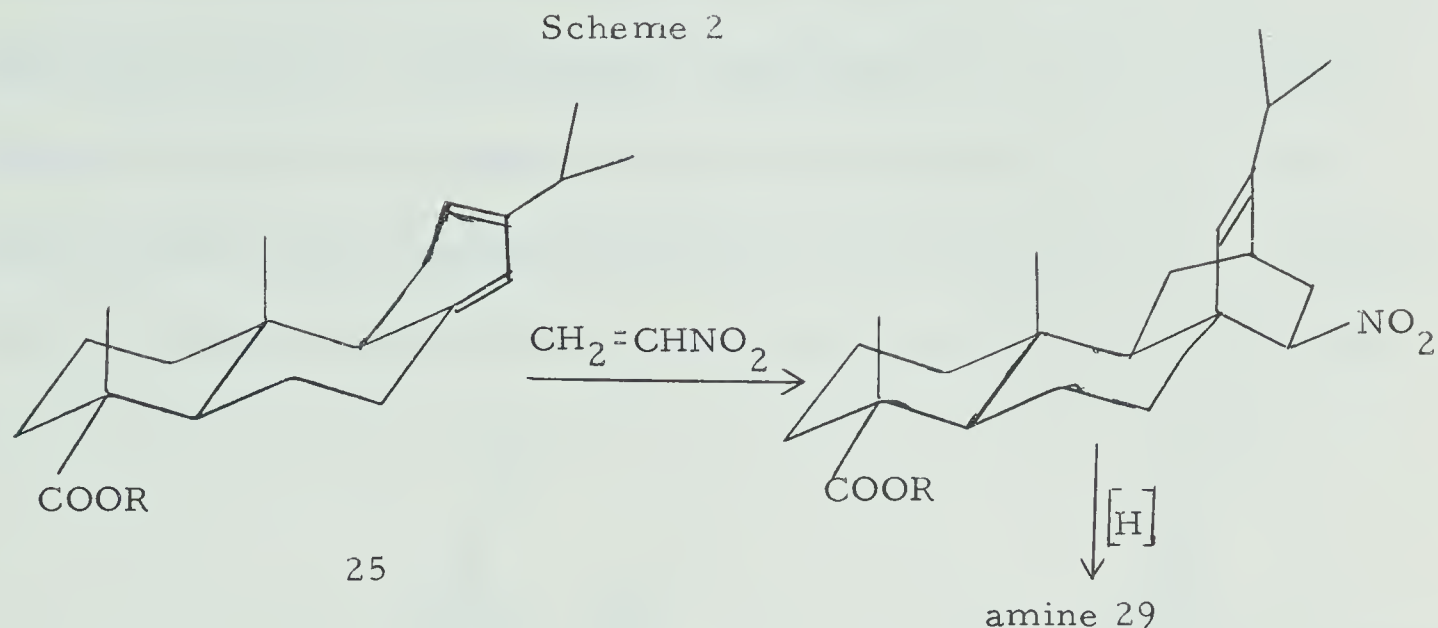
As mentioned in the introductory section, earlier examples illustrating the rearrangement of the bicyclo[2.2.2]octene system to the bicyclo[3.2.1]octene system suggested two possible approaches to the problem. The first approach involves deamination of the amine 29 ($R = CH_3$) and the second involves solvolysis of the arene sulfonate 30 ($X = OTs$, $R = Me$).



The first of these approaches was investigated initially. The synthesis of the amine 29 ($R = CH_3$) was our first objective.

Two routes leading to the formation of the amine 29 can be visualized as shown in schemes (1) and (2).





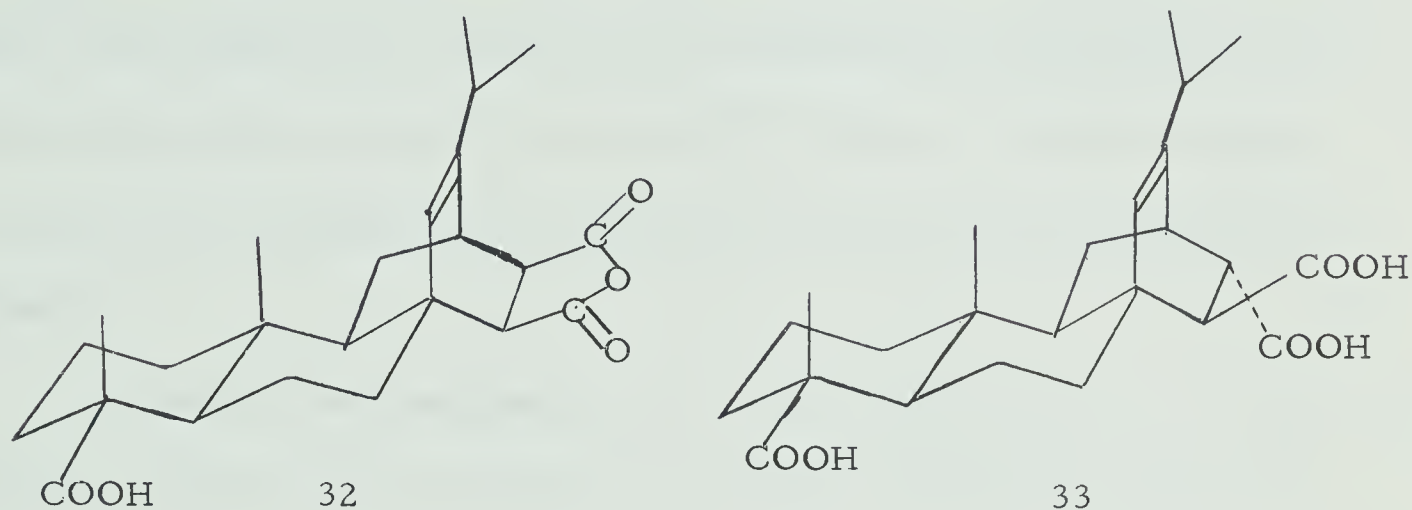
Both schemes involve preparation of a Diels-Alder adduct from levopimaric acid (or its ester) and a dienophile as the first step. The second step in Scheme 1 consists in subjecting the adduct to the Schmidt or the Curtius reaction. In Scheme 2 catalytic or metal-acid reduction of the adduct is required. The reaction sequences indicated in the two schemes are analogous to those used by Goering^{21b}, and Wildman^{21a} in the synthesis of 27. In view of the fact that nitroethylene is not readily available²³ it was decided to adopt the procedure shown in Scheme 1.

PREPARATION OF THE ADDUCT 31 ($\text{R} = \text{CH}_3$)

The first step in the projected synthesis of the amine 29 involves the preparation of the adduct 31 ($\text{R} = \text{CH}_3$) by Diels-Alder reaction of methyl levopimarate (25) ($\text{R} = \text{CH}_3$) with acrylic acid.

At the time this work was initiated (fall of 1963) in this laboratory, preparation of the adduct 31 ($\text{R} = \text{H}$ or CH_3) had not been reported.

Adducts resulting from the reaction of levopimaric acid with other dienophiles were known. For example, maleopimaric acid (32) and fumaropimaric acid (33) were obtained from levopimaric acid by Diels-Alder reaction with maleic anhydride and fumaric acid, respectively. Adducts with acrylonitrile were also known but structures for these had not been

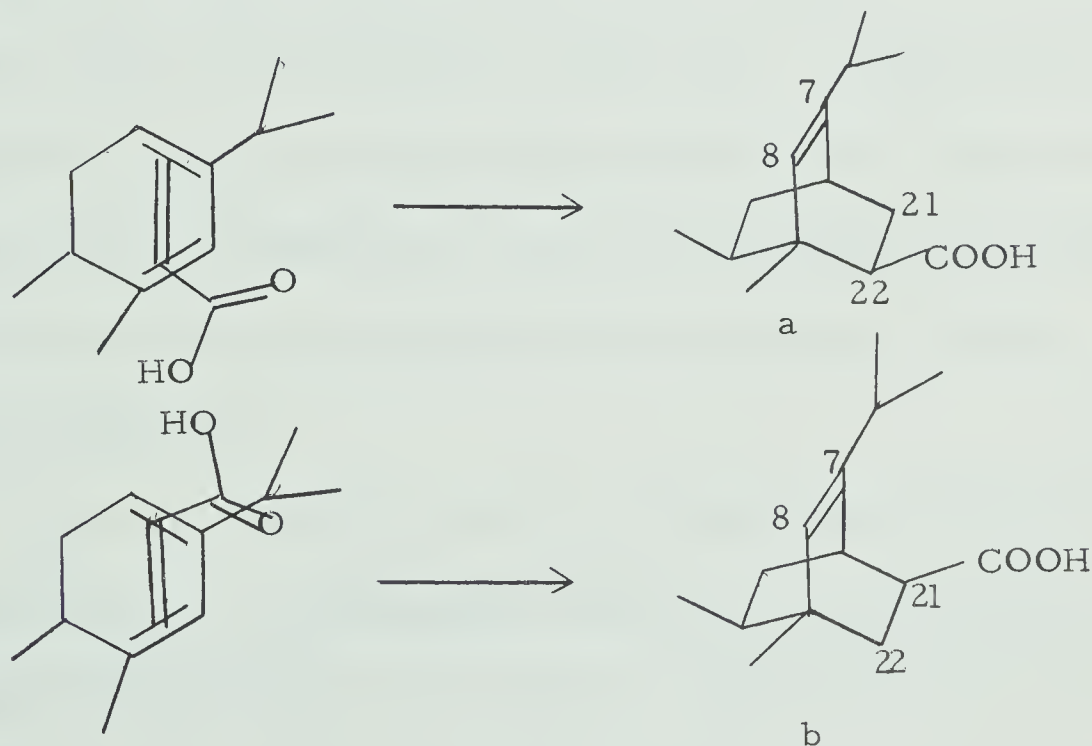


assigned in a definitive manner²⁴. In view of the structural similarity between acrylonitrile and acrylic acid knowledge of the structures for the Diels-Alder adducts of the former substance and levopimaric acid might have been helpful in the present work in predicting the structures of the products. It seemed reasonable however to expect that the compound 31 (C-22 endo carboxyl group) would be the predominant product of the reaction between levopimaric acid (or its ester) and acrylic acid on the basis of the following considerations.

The Diels-Alder reaction of levopimaric acid and maleic anhydride gives maleopimaric acid (32) as the only isolable product although, in principle, four isomeric products may be anticipated. This selectivity has been rationalized in terms of steric and electronic factors. Lloyd

and Hendrik²⁵ have suggested that the approach of a dienophile from the β face (top side) of levopimaric acid is inhibited by the C-12 methyl group of the latter. This hindrance results in exclusive attack by the dienophile on the α face of levopimaric acid. Consequently only two isomeric products are possible. Application of Alders' endo addition rule²⁶ then leads to the prediction that maleopimaric acid (32) will be the major product since in the bicyclo[2.2.2]octene system the endo product is not only kinetically favored but is also thermodynamically favored.

Applying these arguments to the Diels-Alder reaction of levopimaric acid and acrylic acid the two isomeric compounds indicated by part structures a and b would be expected to be the predominant



products. The transition state leading to the formation of isomer 'a' appears to have minimum nonbonded interactions. On this basis

formation of the adduct 31 was expected to be the favored process. This expectation was, in fact, realized as will be evident from the following account.

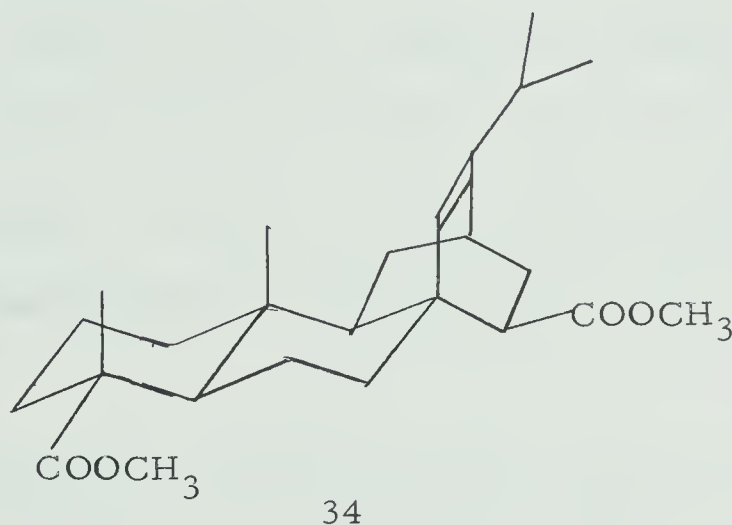
Before the Diels-Alder reaction was effected it was necessary to protect the carboxyl group of levopimaric acid (in view of the subsequent transformation as indicated in Scheme 1). This was achieved by esterification with ethereal diazomethane.

The reaction was carried out by heating under reflux a solution of methyl levopimarate in benzene with an excess of acrylic acid. An acetone solution of the crude product obtained from this reaction was treated with cyclohexylamine to give a crystalline salt. This salt was decomposed by treatment with dilute phosphoric acid to afford the crystalline adduct 31 (R = Me) in ca. 65% yield. Assignment of the structure 31 is based on the following considerations. Elemental analysis of a pure sample (m.p. 166-167°) obtained by recrystallization from Skellysolve B was consistent with the molecular formula $C_{24}H_{36}O_4$ (MW 388).

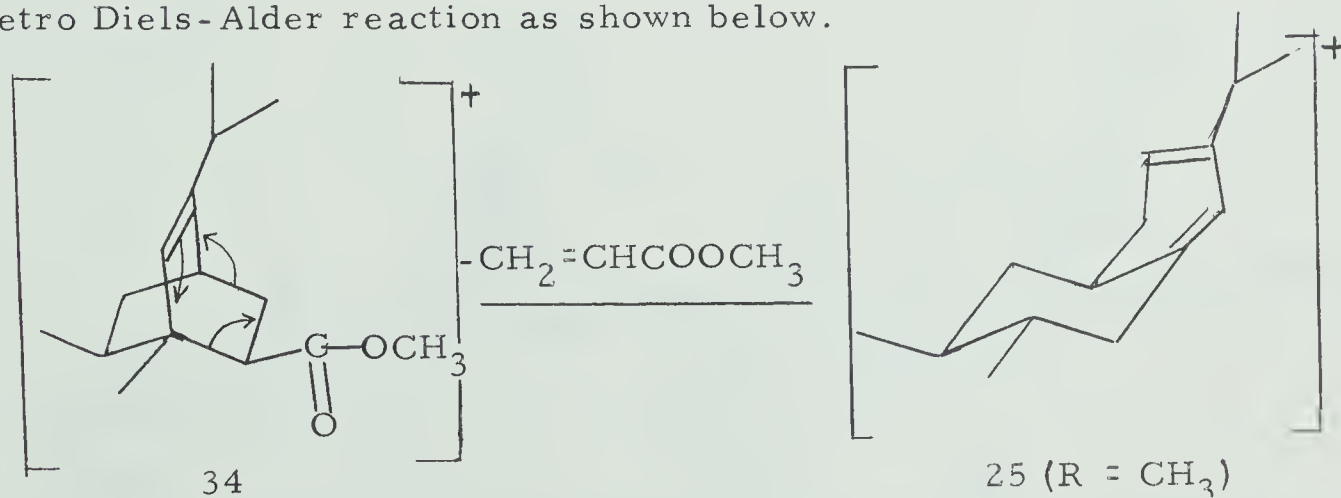
The infrared spectrum shows a strong band at 1720 cm^{-1} assignable to the C-1 carbomethoxy group, and a broad absorption in the region $2400\text{-}3200\text{ cm}^{-1}$ attributable to the C-22 carboxyl group. The presence of these two functions is supported by the signals at τ 6.28 (three protons, singlet $C_1\text{-COOCH}_3$) and τ -0.95 (one proton broad, $C_{22}\text{-COOH}$) in the n.m.r. spectrum. The isopropyl group on

C-7 appears as a six proton doublet at τ 8.95 ($J = 7$ cps). The high field signal at τ 9.38 is attributed to the C-12 methyl group in analogy with the assignment made in maleopimaric acid²⁷. The olefinic proton at C-8 and the methyl group at C-1 resonate at τ 4.57 (singlet) and τ 8.83 respectively.

Further support for the structure 31 ($R = CH_3$) comes from the spectral properties of its methyl ester 34. The mass spectrum of 34



shows the expected molecular ion at m/e 402. A strong peak also appears at m/e 316. The latter can be rationalized in terms of a retro Diels-Alder reaction as shown below.

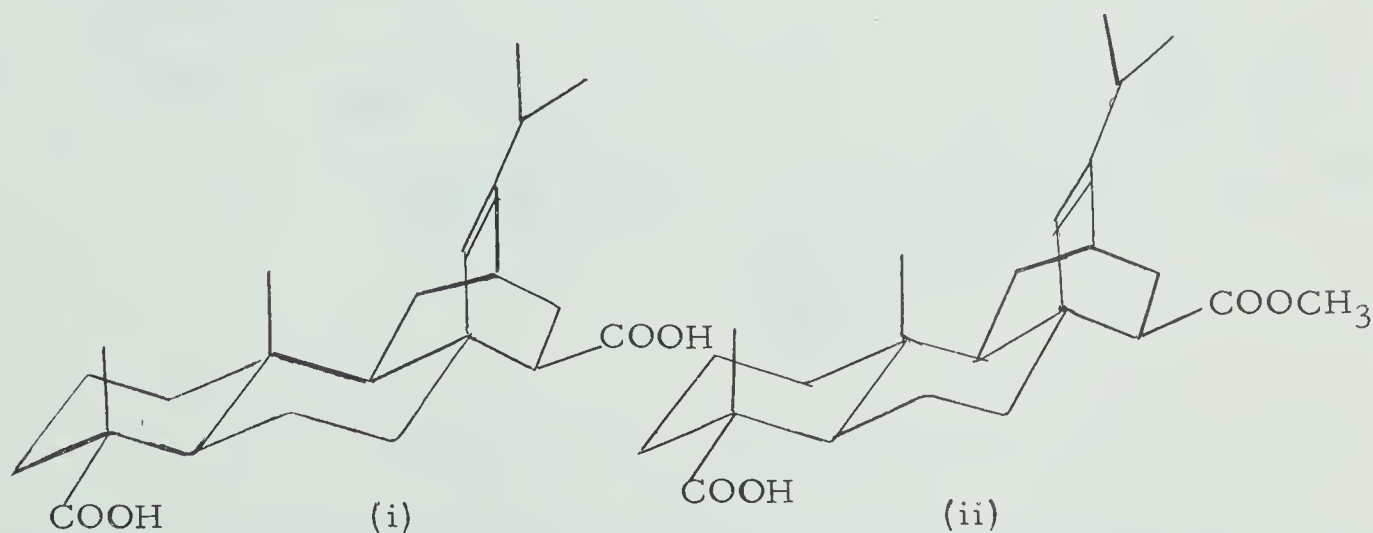


The infrared spectrum of 34 shows a strong band at 1725 cm^{-1} indicating the presence of the ester functions. The n.m.r. spectrum displays

two signals for the methyl groups in the low field region. The signal at τ 6.35 is attributed to the C₁ carbomethoxy group while the one at τ 6.45 is assigned to the C-22 carbomethoxy group. The latter assignment can be rationalized in terms of a shielding effect by the Δ^{7-8} double bond. Other signals in the n.m.r. spectrum are consistent with the formulation as shown in 34.

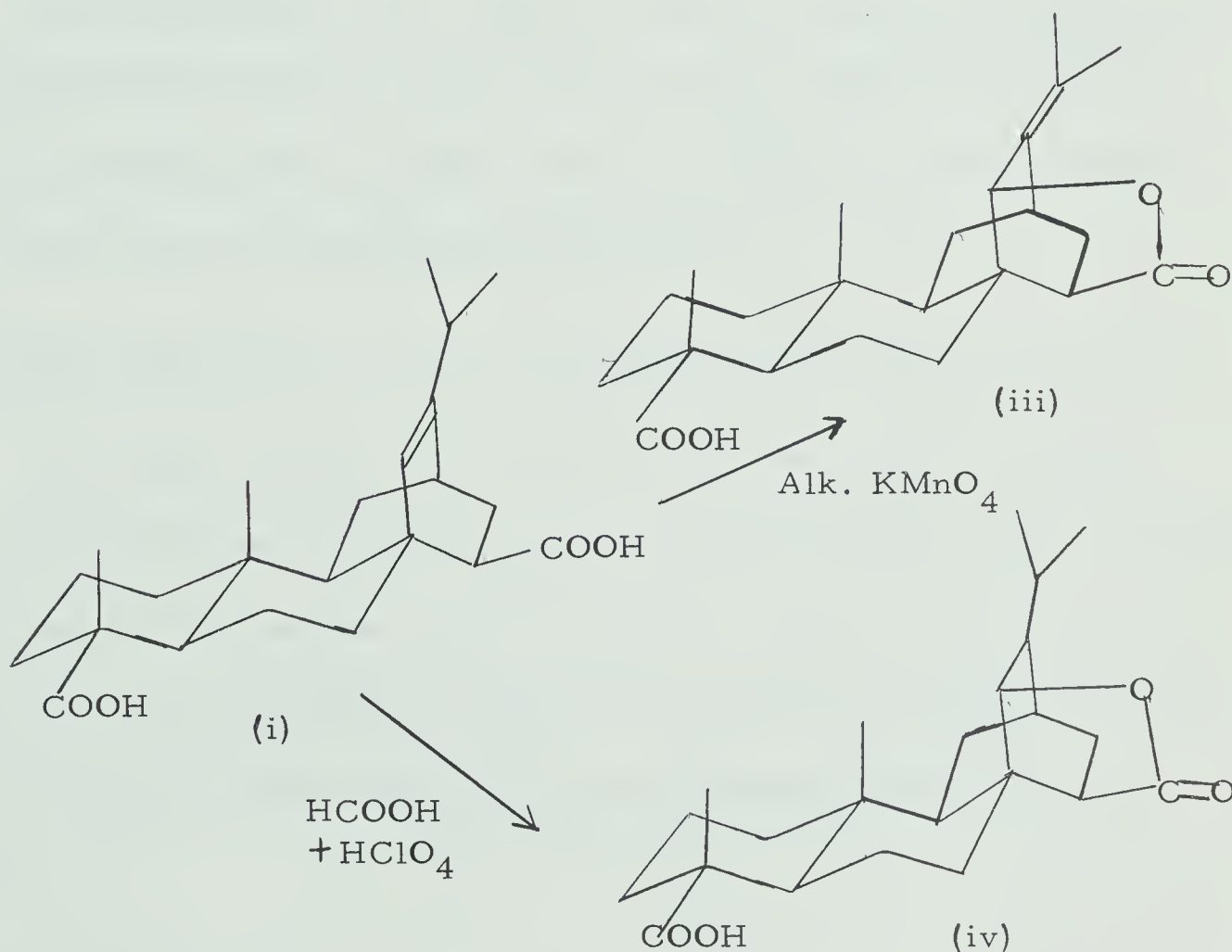
Although the evidence presented so far is consistent with the structure 31 (R = CH₃) it does not permit a definitive assignment for this compound since the C-21 isomer would also conform with the evidence discussed thus far. In order to confirm that the adduct carries a C-22 endo carboxyl group bromolactonization experiments were contemplated.

At this stage Lawrence²⁸ et al reported the isolation of (i) and (ii) from Diels-Alder reactions of levopimaric acid with β -propiolactone and methyl acrylate respectively. The reaction with β -propiolactone



(carried out at 225°) furnished (i) in ca. 57% yield. Compound (ii) was obtained in ca. 90% yield. The high selectivity shown in the formation

of (ii) has been explained by Lawrence et al as due to the lower temperature (about 80°) used for the reaction between levopimaric acid and methyl acrylate. In order to confirm the structural assignment based on spectroscopic evidence, these authors subjected compound (i) to lactonization. The two lactones (iii) and (iv) were formed on treatment with alkaline potassium permanganate and formic acid-perchloric acid respectively. The formation of compounds (iii) and (iv) from (i)



establishes that the carboxyl group in the adduct (i) is endo and located at C-22.

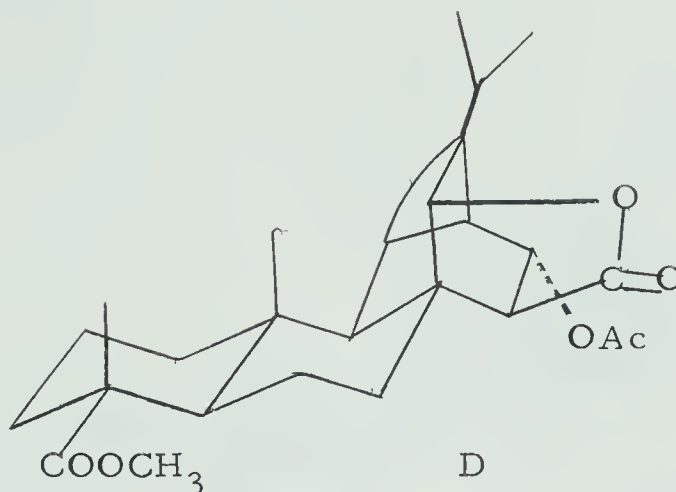
Confirmation of structure 31 ($R = CH_3$) was therefore sought through a correlation with (i). An authentic sample* of (i) was esterified with ethereal diazomethane to afford the dimethyl ester. Comparison (m.p. , m.m.p. , infrared spectrum) of this dimethyl ester with 34 established that the two compounds were identical. Since 34 was obtained by esterification (CH_2N_2) of 31 ($R = CH_3$) the structure for the latter compound is confirmed.

With the adduct 31 ($R = CH_3$) in hand we turned our attention to its transformation into the amine 29 ($R = CH_3$) as shown in Scheme 1. Before considering this transformation the reaction of adduct 31 ($R = CH_3$) with lead tetraacetate will be discussed.

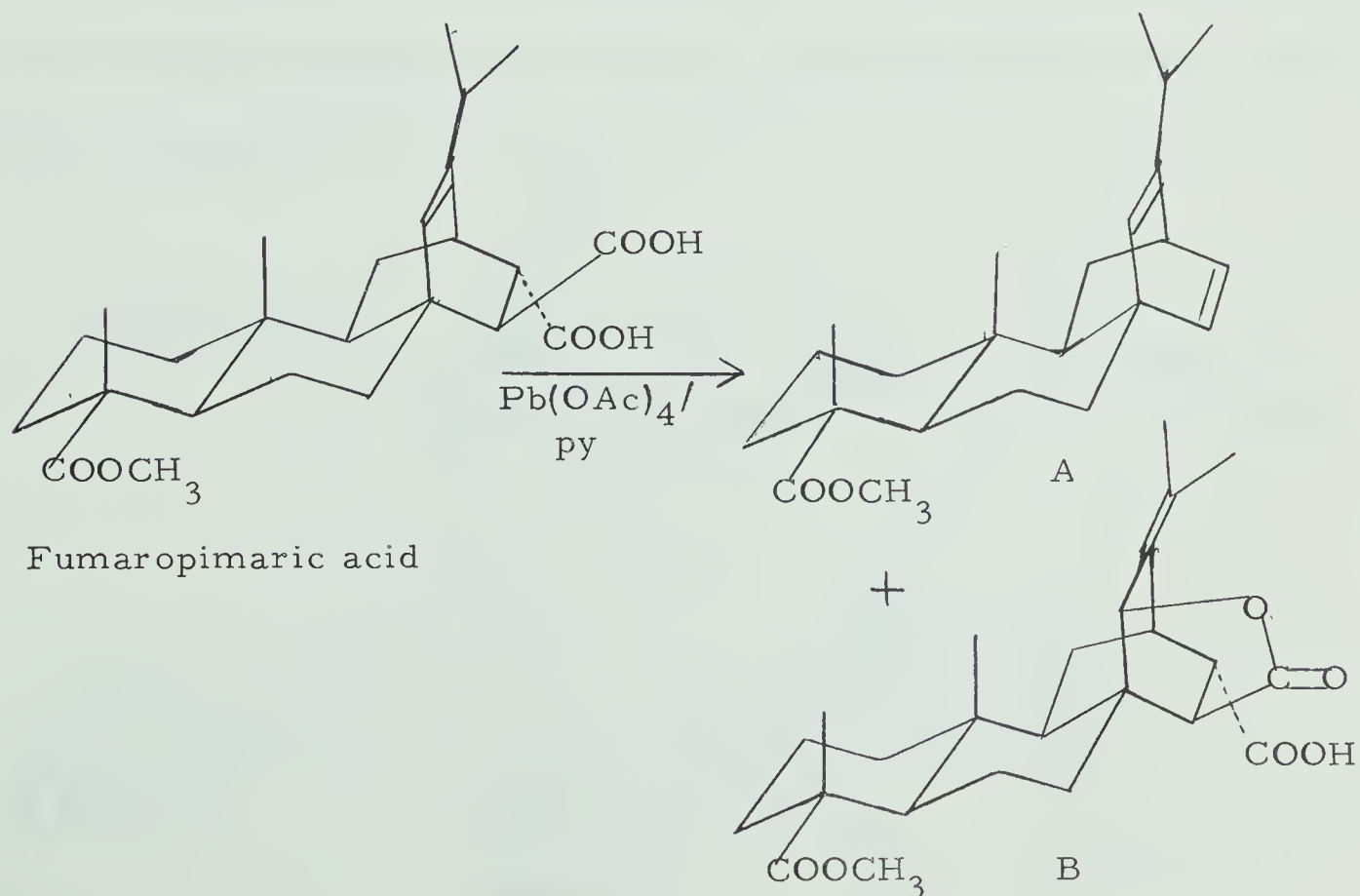
REACTION OF ADDUCT 31 ($R = CH_3$) WITH LEAD TETRAACETATE.

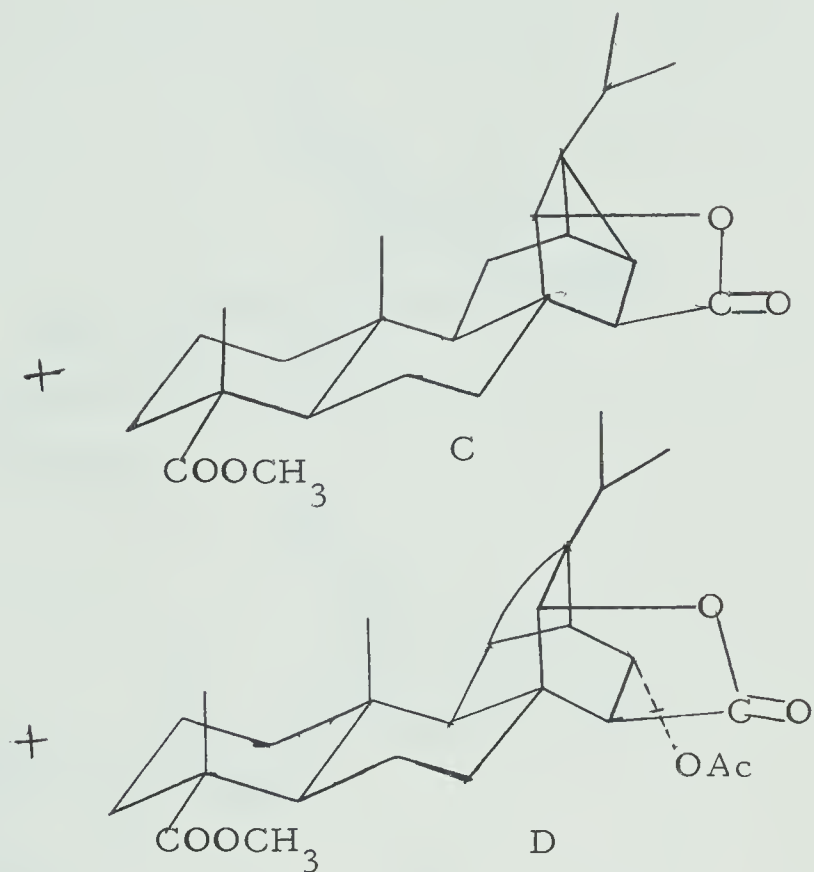
The main interest in the reaction of 31 with lead tetraacetate centered around the mechanistic aspects of the formation of the compound D isolated by McDonald and Ayer²⁹ from the reaction of fumaropimaric acid with lead tetraacetate. Before discussing the mechanistic aspects a brief summary of the origin and structure elucidation of 'D' is in order.

* We wish to thank Dr. R. V. Lawrence for providing an authentic sample of compound (i).

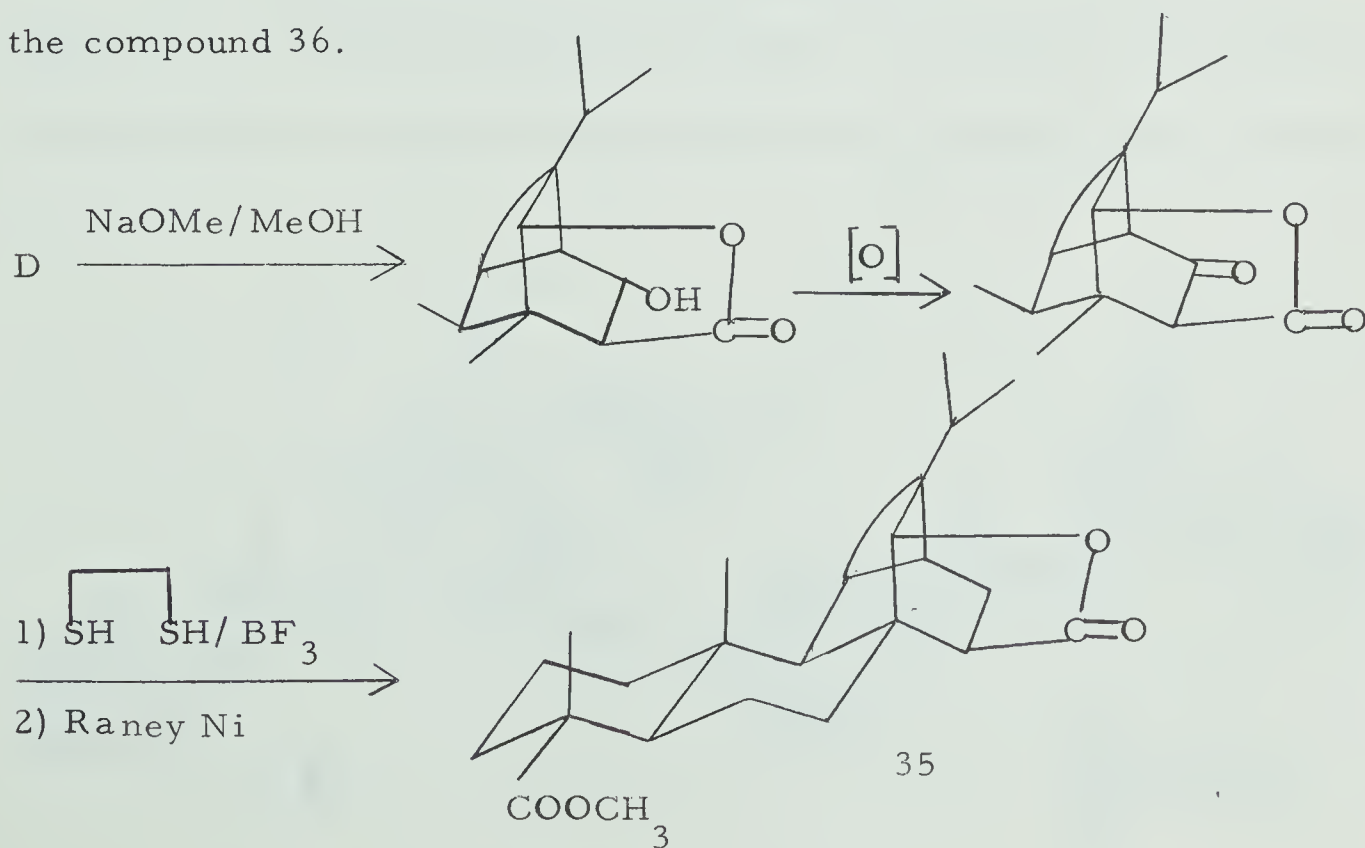


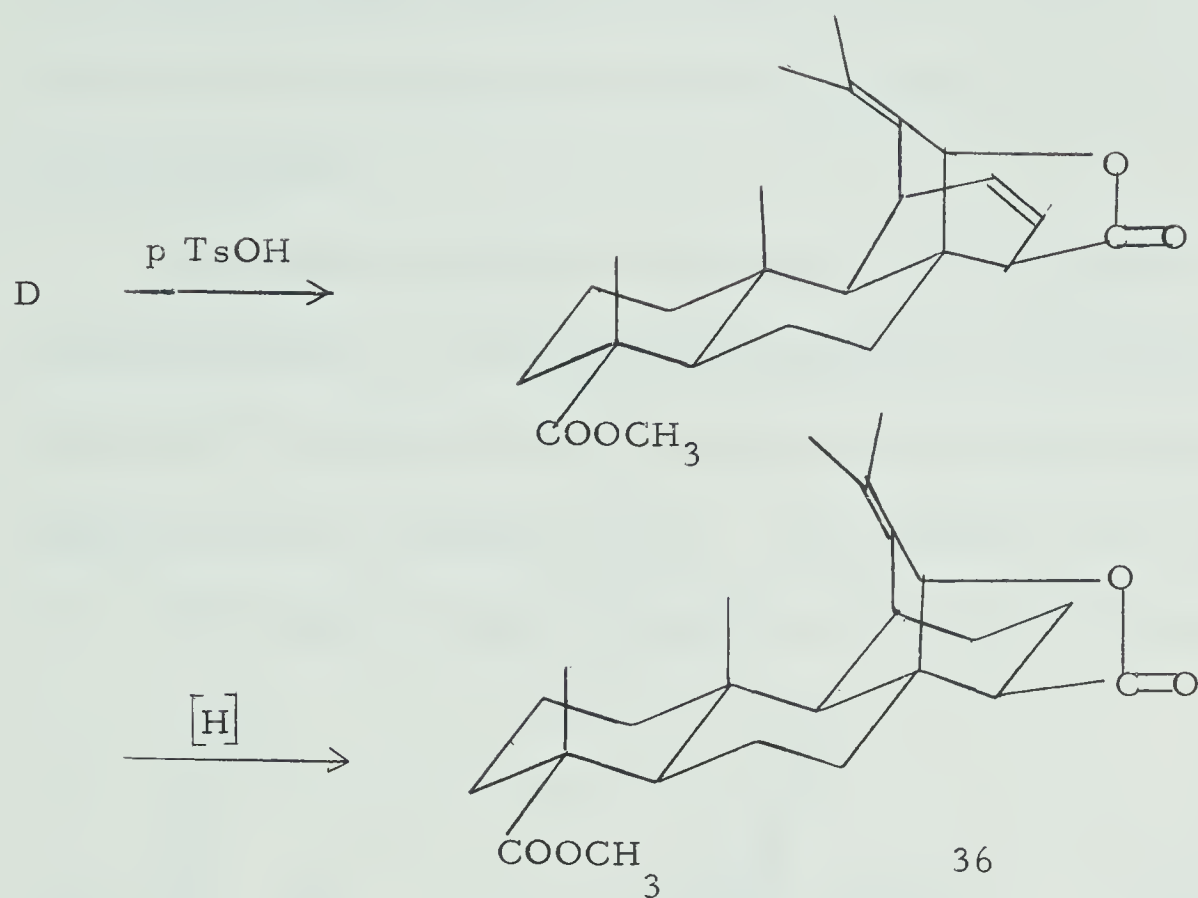
McDonald and Ayer subjected fumaropimaric acid to reaction with lead tetraacetate with the objective of obtaining the bisdecarboxylated product A. Although these workers succeeded in obtaining the compound A the yields were poor because of competitive lactonization reactions. Thus they report isolation of compounds A-D in yields ranging from 3-10%.



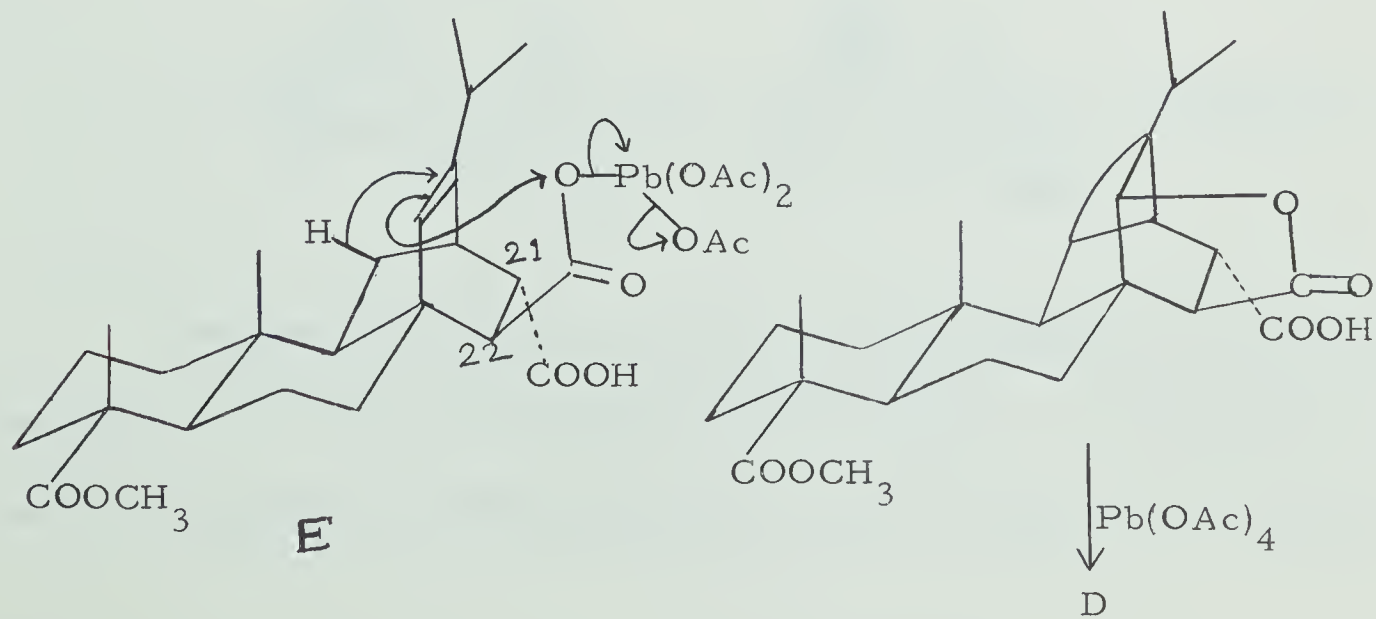


The formation of compound D is interesting from a mechanistic point of view. Chemical evidence in support of structure D comes from the following transformations leading to the cyclopropyl lactone 35 and the compound 36.



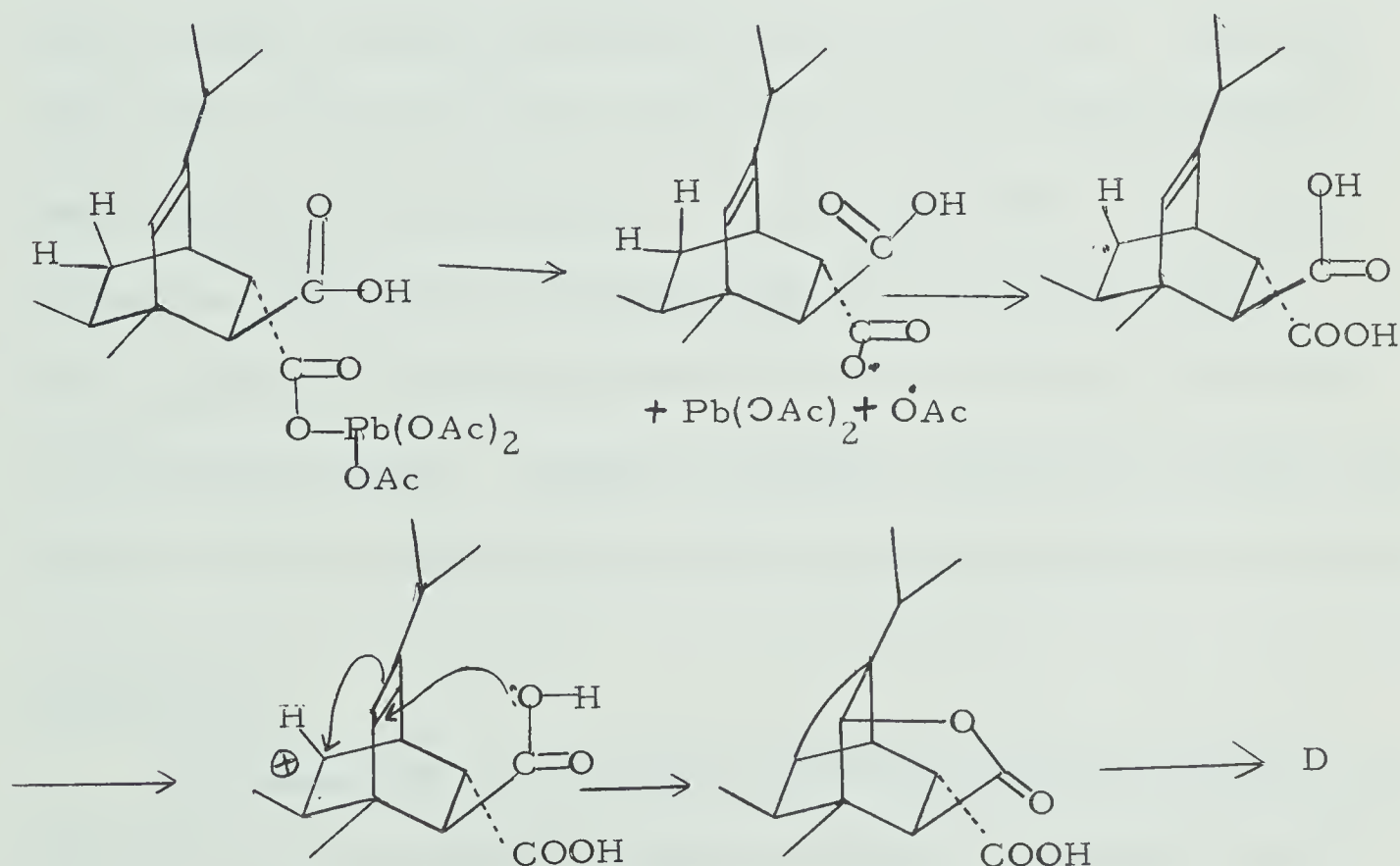


The mechanism proposed for the genesis of compound D is shown in E. The lactonization reaction is presumed to be initiated by the formation of a mixed ester of the C-22 carboxyl group with lead



tetraacetate. Lead diacetate and acetic acid are then eliminated by a concerted sequence shown by the arrows (E). Oxidative replacement of the C-21 carboxyl group by an acetoxy group may precede or follow the lactonization.

Although the proposed mechanism seems plausible its validity remained untested. It is possible to rationalize the formation of compound D in terms of an alternate mechanism which involves participation of the C-21 carboxyl group. One possible way in which the C-21 carboxyl group might participate is shown in the following scheme.



It appeared possible to rule out the last possibility by employing the adduct 31 in the reaction with lead tetraacetate. If a mechanism of the type suggested by McDonald et al is valid the adduct 31 on treatment

with lead tetraacetate would be expected to form the cyclopropyl lactone 35 in analogy with fumaropimaric acid. On the other hand if the mechanism involving the participation of the C-21 carboxyl group is operative compound 35 could not be formed in the reaction of 31 with lead tetraacetate. In fact, this reaction did furnish the cyclopropyl lactone and hence lends support to the mechanism proposed by McDonald and Ayer. In addition to the lactone 35 several other products were isolated from this reaction.

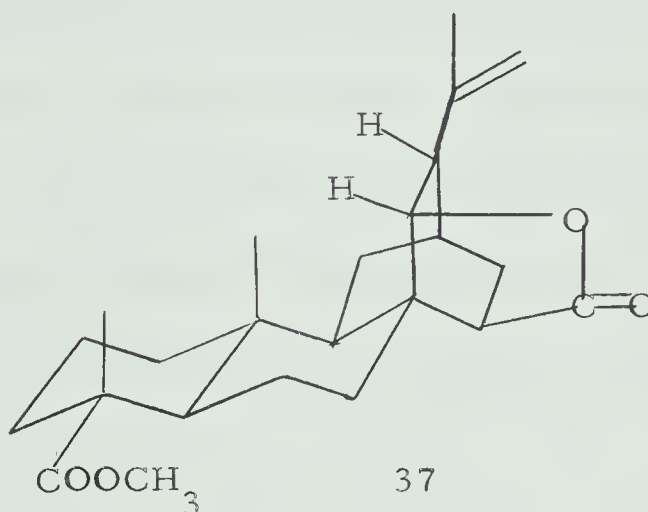
The reaction was carried out by treating the adduct 31 ($R = CH_3$) with an excess of lead tetraacetate in glacial acetic acid. Unchanged adduct was removed from the crude product by extraction with dilute alkali, leaving a neutral product in a yield of ca. 90%. The neutral product was subjected to chromatography on acid washed alumina. Four crystalline compounds I ($\approx 5\%$), II ($\approx 1.1\%$), III ($\approx 1.5\%$) and IV ($\approx 4.1\%$) were isolated. Another crystalline compound, (V, $\approx 9\%$), was obtained when the mother liquor of IV was chromatographed on silica gel.

COMPOUND I

Compound I (m.p. $139-140^\circ$ recrystallized from methanol; m.p. $147-148^\circ$ recrystallized from Skellysolve B) gave a molecular ion at m/e 386 in the mass spectrum. It was identified as the cyclopropyl lactone 35 by comparison with an authentic sample (m.p., m.m.p., IR, NMR).

COMPOUND II

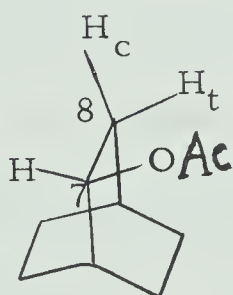
Compound II, which will be referred to as the isopropenyl lactone, was crystallized (m.p. $170-176^{\circ}$) from methanol as colorless needles. It is assigned the structure 37 on the basis of its spectral properties.



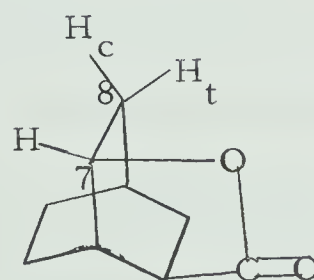
The n.m.r. spectrum of 37 shows only three signals for C-methyl groups. Two of these occur at $\tau 9.07$ (singlet) and $\tau 8.7$ (singlet). The former is assigned to the C-12 methyl and the latter to the C-1 methyl group. The third signal appears at $\tau 8.23$ and is indicative of a methyl group on an unsaturated carbon atom. Two olefinic protons (at $\tau 5.24$ and $\tau 5.12$) fall in the region where protons of a terminal methylene normally resonate.* Considering that the n.m.r. spectrum does not show a doublet signal attributable to an isopropyl group the signals at $\tau 8.23$, $\tau 5.24$ and $\tau 5.12$ can best be accommodated by placing an isopropenyl group on C-7. Support for the presence of the terminal

* The signal at $\tau 5.12$ under high resolution appears as a quartet ($J \approx 1$ cps). The signal at $\tau 8.23$ is a broad singlet. The splitting of only one of the two olefinic protons is suggestive of cisoid allylic coupling.

methylene comes from the absorption bands at 890 cm^{-1} (m), 1640 cm^{-1} (w), 3080 cm^{-1} (w) in the infrared spectrum. The C-1 carbo-methoxy group is easily identified in the infrared spectrum by a strong band at 1720 cm^{-1} and in the n.m.r. spectrum by a three proton signal at $\tau 6.33$. The γ lactone is characterized by a strong band at 1775 cm^{-1} in the infrared spectrum. Closure of the lactone ring at C-8 is inferred from the signal at $\tau 5.34$ (doublet, $J_{7,8} \approx 6$ cps) in the n.m.r. spectrum. This latter coupling indicates that the protons on C-7 and C-8 are cis. The coupling constants of the C-7 proton in bicyclo[2.2.2]octanyl acetate (i) are reported to be $J_{7,8c} = 9$ c.p.s. and $J_{7,8t} = 3$ c.p.s.. Inspection of a molecular model of the corresponding lactone (ii) indicates that closure of the lactone ring affects the dihedral angles $\phi_{7H,8Hc} (> 0^\circ)$ and $\phi_{7H,8Ht} (< 120^\circ)$. Such a change in the dihedral angles might be expected to decrease both cis and trans coupling constants.



(i)

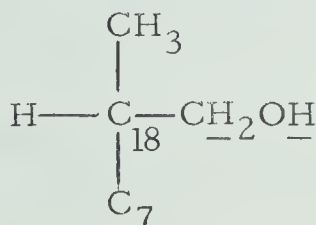


(ii)

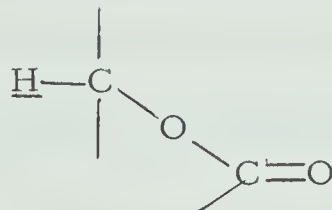
Applying these arguments to the case of isopropenyl lactone 37, the coupling constant of 6 cps favors a cis relationship between the protons on C-7 and C-8.

COMPOUND III

Compound III (m.p. 207-211^o, crystallized from ether) appears from its spectral properties to be a hydroxy lactone. The hydroxyl, lactonic and carbomethoxy functions are indicated by the bands in the infrared spectrum at 3400-3500 cm⁻¹ (H bonded), 1750 cm⁻¹ and 1715 cm⁻¹ respectively. The band attributed to the lactone group appears at relatively lower frequency and may be indicative of a hydrogen bonded γ lactone. The nature of this hydrogen-bonding was not determined. The n.m.r. spectrum of compound III exhibits signals at τ 9.09 (3H, singlet), τ 8.78 (3H, singlet), τ 8.7 (3H, d, J = 4 c.p.s.), τ 7.58 (1.5-2H, broad singlet), τ 6.45 (2H, complex multiplet), τ 6.33 (3H, singlet), τ 5.30 (1H, doublet of doublets, J = 5 and 3.5 c.p.s.). The signal at τ 7.58 disappears when the spectrum is determined after the sample is shaken with D₂O. For this reason it is attributed to the proton(s) on the hydroxyl group(s). Whether compound III contains one hydroxyl group or two hydroxyl groups is not certain. The signal at τ 5.3 collapses to a doublet (J = 3.5 c.p.s.) on simultaneous irradiation 196 c.p.s. downfield from tetramethylsilane. Since the n.m.r. spectrum does not show a signal assignable to an isopropyl group on C-7 it seems reasonable to attribute the signals at τ 8.7, 7.58 and 6.45 to a group such as



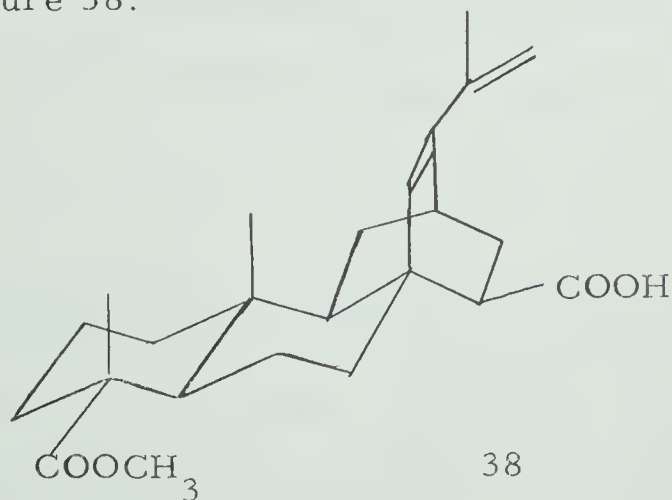
(CH₃ at τ 8.7, CH₂ at τ 6.45 and OH at τ 7.58). In analogy with other compounds in the series the signal at τ 5.30 can be attributed to the proton geminal to the lactone function as indicated in the



accompanying part structure. Exact location of the site of closure of the lactone ring is, however, in doubt. The mass spectrum of compound III showed the ion of highest mass at m/e 389 and a strong peak at m/e 371 which presumably arises from the former by loss of H_2O . A definitive assignment of the molecular formula from this information was not possible. Since the available data are insufficient no definite structure could be assigned to compound III. Chemical degradations were not attempted since compound III was not available in sufficient quantity.

COMPOUND IV

Compound IV (m.p. 163-166^o, crystallized from Skellysolve B-benzene) is assigned structure 38.

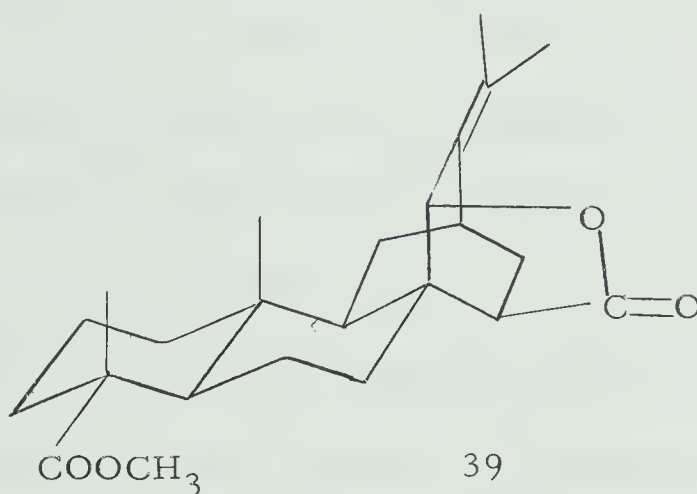


The conjugated diene system was indicated by strong absorption in the ultraviolet spectrum at $242 \text{ m}\mu$ ($\epsilon = 26,000$). More information about the diene system was gained from the infrared and the n.m.r. spectra. The former contains bands characteristic of a terminal methylene group (880 cm^{-1}) and of a conjugated diene system (1620 cm^{-1} and 1665 cm^{-1}). The n.m.r. spectrum shows three olefinic protons, at $\tau 4.15$, $\tau 4.99$ and $\tau 5.25$. The signal at $\tau 4.15$ is assigned to the proton on C-8 and the signals at $\tau 4.99$ and $\tau 5.25$ are attributed to the protons of the terminal methylene. The C-12 and the C-1 methyl protons resonate at $\tau 9.41$ and $\tau 8.83$ respectively. The protons on C-19 appear, as expected for their allylic position, at lower field ($\tau 8.08$). The presence of the carboxyl group on C-22 is indicated by bands at 1700 cm^{-1} and $2400\text{-}3200 \text{ cm}^{-1}$ (broad) in the infrared spectrum. The carbomethoxy group on C-1 is characterized in the infrared spectrum by a strong band at 1720 cm^{-1} and in the n.m.r. spectrum by a three-proton singlet at $\tau 6.35$. The molecular formula ($\text{C}_{24}\text{H}_{34}\text{O}_4$, MW 386) for 38 was confirmed by mass spectrometry. The methyl ester, obtained by treatment of 38 with ethereal diazomethane gave, as expected, a molecular ion at m/e 400 in the mass spectrum.

COMPOUND V.

Compound V was obtained from the mother liquors of compound IV (i.e. 38) by chromatography on silica gel. Initially the infrared spectrum of the mother liquors showed compound V as a minor component.

However, on standing for a few days the composition of the mother liquors changed and compound V appeared to be a major component (inferred from the infrared spectrum). This change aroused suspicion as to whether compound IV was being transformed into compound V in solution. (It appears that compound IV originates from compound V by a reaction catalyzed by acid washed alumina. If allowed to stand in solution compound IV is converted back into compound V, see later). Compound V, which will be referred to as the isopropylidene lactone, is assigned structure 39 on the basis of the following considerations.



The infrared spectrum shows bands at 1660 cm^{-1} ($\text{C}=\text{C}$), 1720 cm^{-1} ($\text{C}-\overset{\text{O}}{\parallel}\text{COMe}$) and 1770 cm^{-1} (γ lactone). In the n.m.r. spectrum the methyl group on C-1 appears at $\tau 8.83$ and the one on C-12 resonates at $\tau 9.28$. The latter signal is indicative of a shielding effect by the Δ^{7-18} double bond²⁷. Displacement of the double bond from its original position (Δ^{7-8}) to the new position (Δ^{7-18}) is supported by the appearance of signals at $\tau 8.25$ and $\tau 8.21$ attributable to the methyl groups on C-18. The C-8 proton geminal to the lactone function

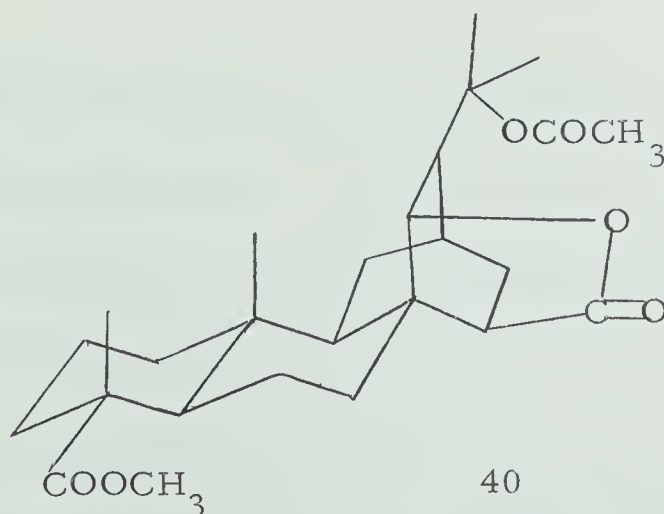
resonates at τ 4.99. This signal occurs at relatively lower field as compared to the values observed for analogous protons in the other lactones considered earlier. The occurrence of the signal at lower field can be rationalized in terms of a deshielding effect on the C-8 proton by the \triangle^{7-18} double bond. Lawrence²⁸ et al and Ayer²⁹ et al have reported n.m.r. spectra for compounds analogous to 39. The n.m.r. spectrum of the latter is comparable to those published by these authors.

Hydrogenation of 39 over Adams' catalyst produced adduct 31 (R = CH₃) as indicated by the n.m.r. spectrum of the product.

Of the five compounds described so far, compound 38 requires further comment. This acidic compound was isolated from chromatography of neutral material on acid washed alumina. Formation of 38 from its neutral precursor must be attributed to a reaction on the adsorbent. Apparently the isopropenyl lactone 37 also arises from its precursor by reaction on acid washed alumina since the n.m.r. spectrum of the product obtained directly from the reaction of adduct 31 (R = CH₃) with lead tetraacetate does not show any signals characteristic of 37. The n.m.r. spectrum however contains signals in the region (τ 8.00) where methyl groups α to carbonyl functions are normally observed. The presence of a band at 1370 cm⁻¹ in the infrared spectrum of the product of the reaction with lead tetraacetate and a consideration of the nature of this reaction suggested the presence of an acetoxy group in the original product. Chromatography on acid

washed alumina did not furnish any compound which carried an acetoxy group. A possible reason for the failure to isolate such a compound may be its transformation into some other substance, possibly into the isopropenyl lactone 37.

In the hope that the transformations caused by acid washed alumina might be avoided by using a different adsorbent, chromatography of the product from the reaction with lead tetraacetate was carried out on silica gel. Compounds 35 and 39 were isolated in ca. 9 and 18% yield respectively. In addition to these two compounds material rich in a third compound was obtained from the chromatography on silica gel. The n.m.r. spectrum of this material displayed signals at τ 8.10 and 7.99. It was subjected to further chromatography on silica gel, which resulted in the isolation of the third compound in ca. 2% overall yield. This compound (m.p. $180-183^{\circ}$, crystallized from ether), which will be referred to as the acetoxylactone, is assigned structure 40 on the basis of the following evidence.

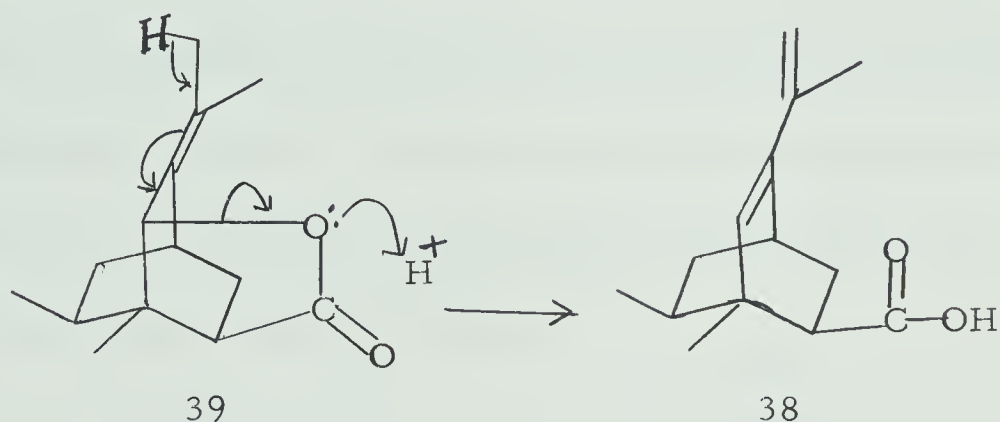


The mass spectrum of compound 40 showed the ion of highest mass at m/e 386 which clearly cannot be the molecular ion if the proposed structure is right. In the light of the information revealed by the infrared and the n.m.r. spectra the ion at m/e 386 can be rationalized in terms of loss of acetic acid from the parent ion. The infrared spectrum contains bands at 1365 cm^{-1} (medium, symmetric in-plane bending mode of $\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_3$), 1720 cm^{-1} ($\text{C}-1\text{ COOCH}_3$ and OCOCH_3) and 1780 cm^{-1} (γ lactone). The methyl groups on C-12 and C-1 appear in the n.m.r. spectrum at τ 9.09 and τ 8.78 respectively. The spectrum does not show the doublet signal expected for an isopropyl group. Instead a six proton singlet at τ 8.39 is apparent. The relatively lower chemical shift for the C-18 methyls can be explained if an acetoxy group is placed on C-18. The n.m.r. spectrum indicates the presence of the latter by the appearance of a three-proton singlet at τ 8.03. Finally the C-8 proton geminal to the lactone function is characterized in the n.m.r. spectrum by a signal at τ 5.40 (doublet, $J = 6\text{ c.p.s.}$).

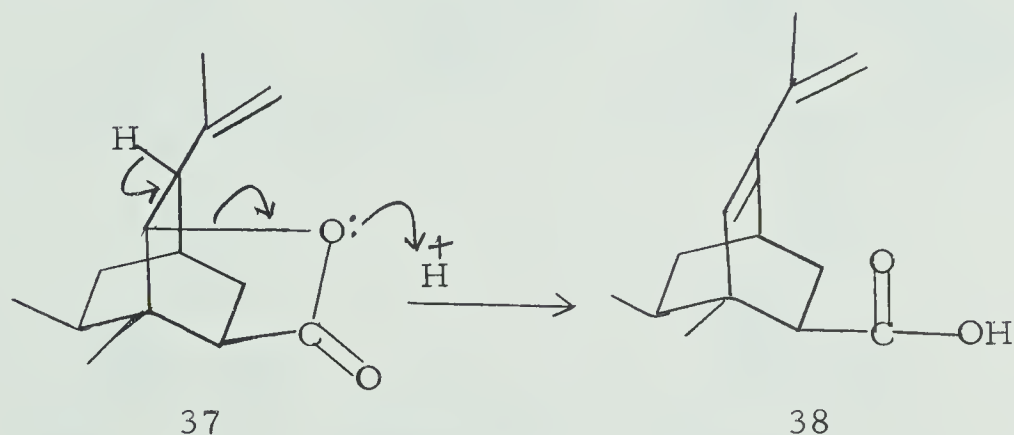
Chromatography on silica gel did not furnish isopropenyl lactone 37 or acid 38. On the other hand the acetoxy lactone 40 could not be isolated from the chromatography carried out on acid washed alumina. Presumably lactone 40 is transformed into lactone 37 on the latter adsorbent. Support for this view comes from the fact that when fractions rich in acetoxy lactone (obtained by chromatography on silica gel) are

chromatographed on alumina compound 37 is isolated.

Formation of the acid 38 from the isopropylidene lactone 39 on acid washed alumina can be rationalized in terms of a protonation-deprotonation sequence as indicated below:

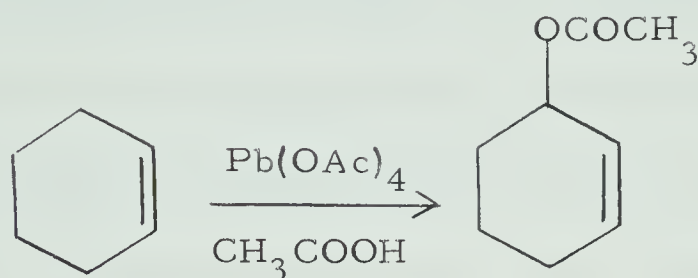


Alternatively 38 may arise from 37 by a similar process as shown.

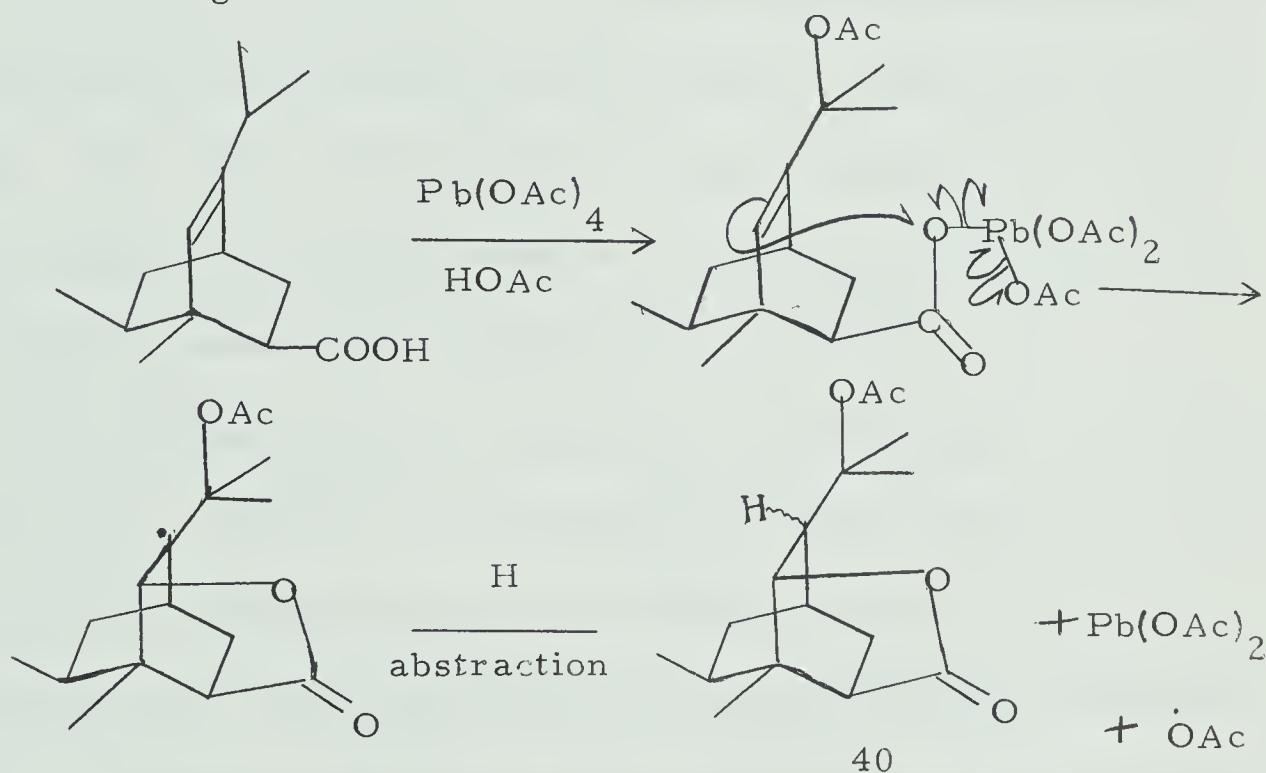


The cyclopropyl lactone 35, isopropylidene lactone 37 and acetoxy lactone 40 thus appear to be the main products formed in the reaction of adduct 31 ($R = CH_3$) with lead tetraacetate. Of these three compounds the acetoxy lactone deserves comment with regard to its formation. Lead tetraacetate is known³⁰ to react with olefins by vicinal addition of acetoxy groups or by replacement of allylic hydrogen with an acetoxy group. The latter type of reaction is illustrated by the reaction of cyclohexene which on treatment with lead tetraacetate gives cyclohexenyl

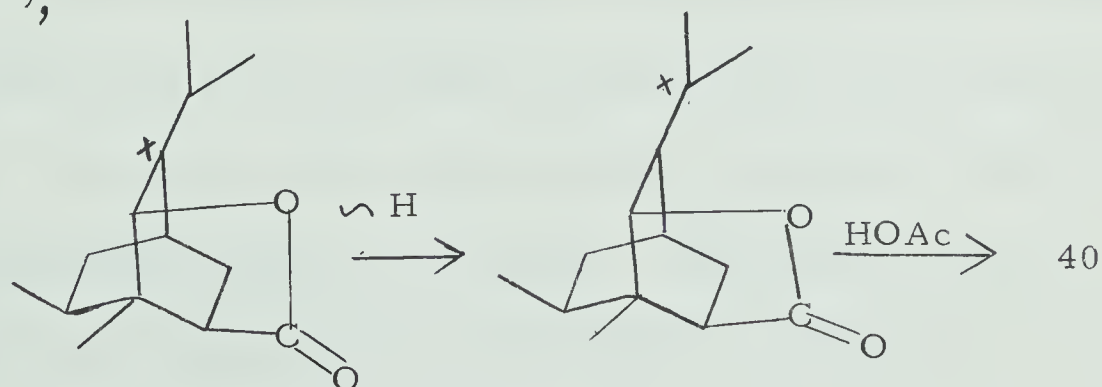
acetate in 35% yield.



In the absence of allylic (or other) activation replacement of hydrogen by acetoxyl does not occur. Acetoxy lactone 40 may arise by substitution of the C-18 hydrogen with an acetoxy group followed by closure of the lactone ring as indicated below:



Alternatively,



Isolation of the cyclopropyl lactone 35 from the reaction of adduct 31 ($\text{R} = \text{CH}_3$) with lead tetraacetate lends support to a mechanism

of the type proposed by McDonald and Ayer. As mentioned earlier these authors obtained 35 from compound D by chemical degradation undertaken for the purpose of confirming the structure assigned to the latter compound. They presented further proof in support of this structural assignment by converting compound D into compound 36. A further transformation of 36 into 41, which substantiates the structure proposed for the former will now be described.

The structural features of compound 36 suggested the possibility of its conversion into a hydroxy acid (or ester) by opening the lactone function. Since this acid would have the hydroxyl group in an allylic position it appeared possible to detect this feature by oxidation of the allylic hydroxyl function to an α, β unsaturated ketone.

In an earlier experiment compound 36 was subjected to Zemplen methanolysis. Isolation of the hydroxy acid which resulted from this reaction was not satisfactory since the product tended to relactonize during work-up. Treatment of 36 with sodium methoxide in dimethyl sulfoxide afforded in satisfactory yield a crystalline substance which was identified as the hydroxy sodium dicarboxylate from its spectral properties. In order to avoid relactonization, attempts to obtain the hydroxy dicarboxylic acid were not made. The hydroxy sodium dicarboxylate was subjected to Sarett oxidation³¹ and the product obtained from this oxidation reaction was esterified with ethereal diazomethane. Sublimation of the esterified product furnished a crystalline compound

The first part of the paper discusses the importance of the study and the objectives of the research. It also outlines the methodology used in the study and the results obtained. The second part of the paper discusses the implications of the study and the conclusions drawn from the research. It also provides a summary of the findings and a list of references.

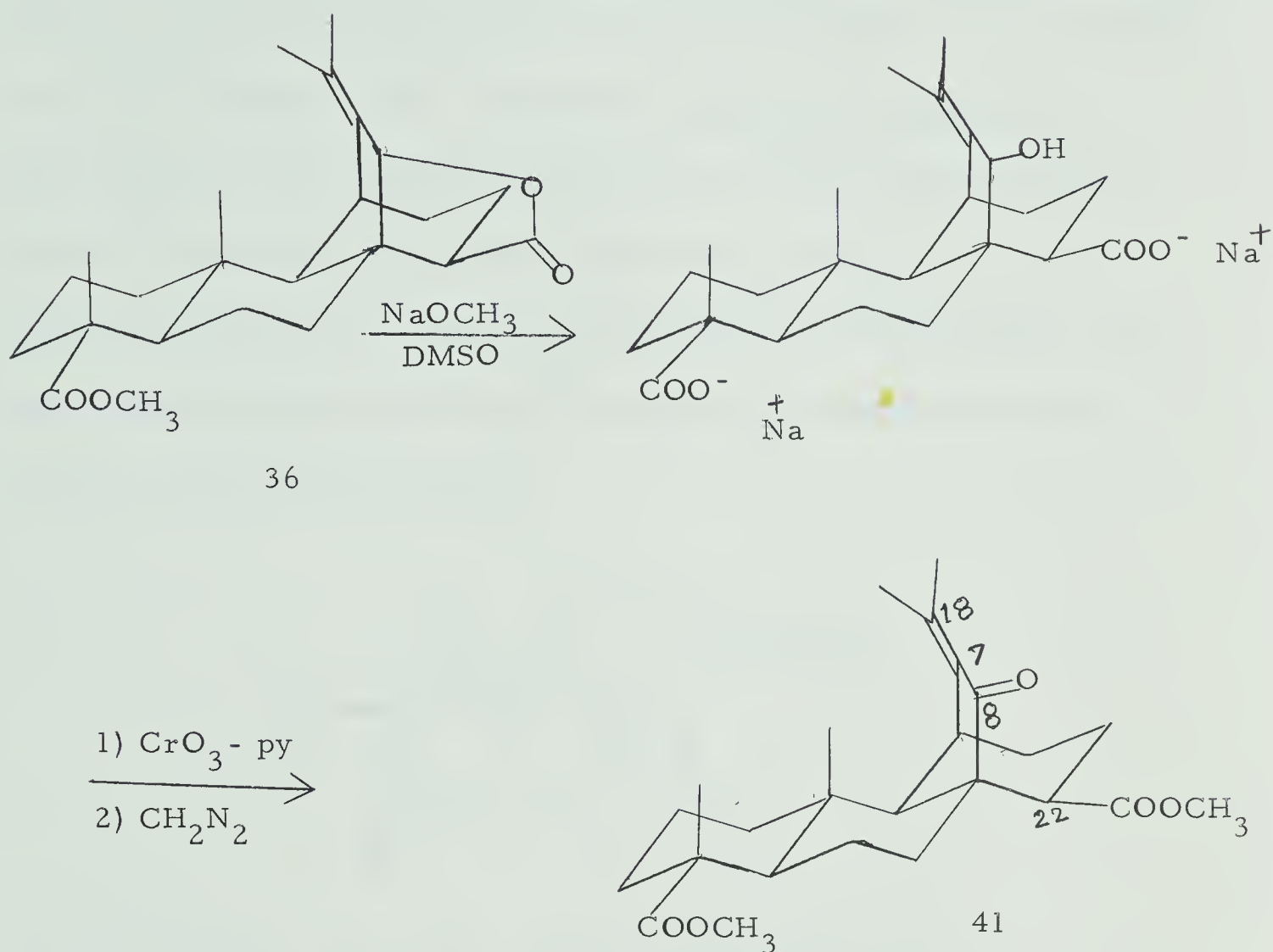
The study was conducted in a laboratory setting and involved the use of a series of tests to measure the performance of the system. The results of the tests were compared to the theoretical predictions and the conclusions drawn from the research. The study found that the system performed well under the conditions tested and that the theoretical predictions were generally accurate.

The implications of the study are that the system can be used in a variety of applications and that the theoretical predictions can be used to guide the design of the system. The conclusions drawn from the research are that the system is a viable option for the application and that the theoretical predictions are a useful tool for the design of the system.

The study was conducted in a laboratory setting and involved the use of a series of tests to measure the performance of the system. The results of the tests were compared to the theoretical predictions and the conclusions drawn from the research. The study found that the system performed well under the conditions tested and that the theoretical predictions were generally accurate.

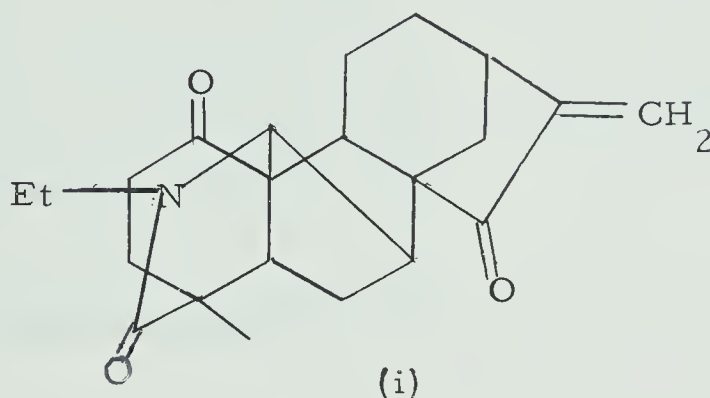
The implications of the study are that the system can be used in a variety of applications and that the theoretical predictions can be used to guide the design of the system. The conclusions drawn from the research are that the system is a viable option for the application and that the theoretical predictions are a useful tool for the design of the system.

(m.p. 174-175^o, recrystallized from Skellysolve B) whose properties are consistent with the expected structure 41.



The compound shows a molecular ion at m/e 416 in agreement with the molecular formula $C_{25}H_{36}O_5$. The infrared spectrum (nujol) contains three bands in the carbonyl region. The bands at 1720 cm^{-1} and 1740 cm^{-1} are assigned to the C-1 carbomethoxy and C-22 carbomethoxy groups respectively(?) The latter assignment is based on the assumption that the dipolar interaction between $\begin{array}{c} \diagup \\ C=O \\ \diagdown \end{array}$ and $\begin{array}{c} O \\ || \\ C-OCH_3 \end{array}$ would enhance the frequency of the stretching mode of the C-22 carbonyl function. The third band in the carbonyl region

occurs at 1700 cm^{-1} and is attributed to the α,β unsaturated ketone in the five membered ring. The cisoid nature³² of the α,β unsaturated ketone is revealed by a relatively strong band at 1625 cm^{-1} attributable to the Δ^{7-18} double bond. Absorption in the ultraviolet spectrum at $260\text{ m}\mu$ ($\epsilon = 11,370$) confirmed the presence of the conjugated ketone. The u.v. absorption values observed for this compound are in fair agreement with the u.v. absorption reported^{3a} for (i) (obtained from deoxysongorine) after allowance³³ is made for the presence of two β -alkyl substituents ($+24\text{ m}\mu$).



Reported values: u.v. max $233\text{ m}\mu$ ($\log \epsilon 4.17$)

(for conjugated ketone in the five membered ring)

The n.m.r. spectrum of 41 is consistent with the proposed structure. The methyl groups on C-12 and C-1 resonate at $\tau 9.38$ and $\tau 8.90$ respectively. The isopropylidene methyl groups appear at $\tau 8.13$ and 7.74 . The latter signal is slightly broadened and its occurrence at lower field is indicative of a greater deshielding effect by the ketonic carbonyl function. This fact permits the assignment of

this signal to C-19 protons which are cisoid to the ketone function.

The fact that the signal at $\tau 7.78$ is relatively broad³⁴ can be rationalized in terms of homoallylic coupling with the C-5 proton since couplings of this type are known to be greater for transoid than cisoid systems.

The presence of two carbomethoxyls in 41 is deduced from the signals at $\tau 6.38$ and $\tau 6.35$ in the n.m.r. spectrum.

Isolation of compound 41 thus favors the structure assigned to compound 36 which in turn supports the structure proposed by McDonald and Ayer for compound D. With these remarks discussion concerning the products of the reaction of adduct 31 with lead tetraacetate is concluded. The next section describes transformation of the adduct 31 ($R = CH_3$) to the amine 29 ($R = CH_3$).

TRANSFORMATION OF ADDUCT 31 ($R = CH_3$) TO THE AMINE 29 ($R = CH_3$).

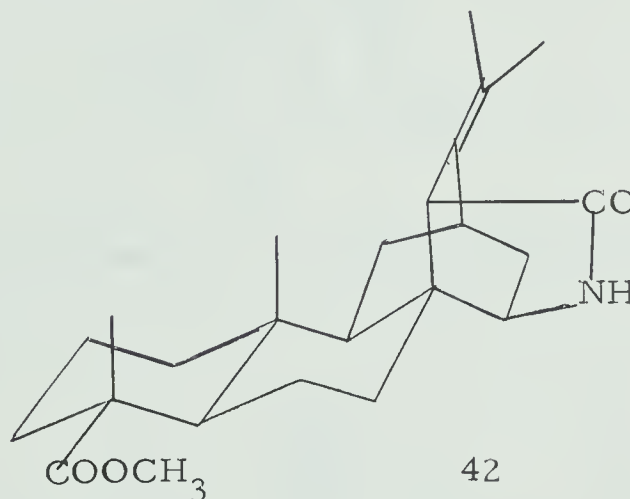
The Schmidt³⁵ and the Curtius reactions have been extensively used to bring about the transformation of a carboxyl group into an amino group. Although the two reactions are similar in principle they vary considerably in experimental detail. Compared to the Curtius reaction the Schmidt reaction is a simpler procedure. The latter reaction is carried out in one step and isolation of intermediates is not required. Furthermore in many instances the Schmidt reaction is known to produce amino compounds in better yields. For these reasons it was decided to adopt this procedure in the conversion of

adduct 31 ($R = CH_3$) to amine 29 ($R = CH_3$).

a) Attempted conversion of adduct 31 ($R = CH_3$) to amine 29 ($R = CH_3$) by the Schmidt reaction.

Following the standard procedure³⁵ adduct 31 ($R = CH_3$) and hydrazoic acid (chloroform solution) were allowed to react in the presence of concentrated sulfuric acid. The reaction mixture was then diluted with water and the chloroform layer was separated from the aqueous acidic layer. The latter was then basified with sodium carbonate and extracted with ether. The ether extract gave a basic product in ca. 11% yield after removal of the solvent. The chloroform layer on evaporation afforded nonbasic material in ca. 72% yield. Thus, the Schmidt reaction did not appear satisfactory from the point of view of the preparation of amine 29 ($R = CH_3$). The poor yield in which the basic product was obtained suggested that the reaction was mainly taking a course other than the one expected to lead to amine 29 ($R = CH_3$). In order to gain more information about this aspect the nonbasic material obtained from the Schmidt reaction was examined. The infrared spectrum of this material indicated the presence of a carboxyl group as judged from the broad absorption in the region 2400-3100 cm^{-1} and the presence of a band at 1705 cm^{-1} . In addition, two other strong bands in the region 1695-1720 cm^{-1} and two weak bands in the region 3200-3450 cm^{-1} were observed. The nonbasic product was treated with ethereal diazomethane in order to convert the acidic

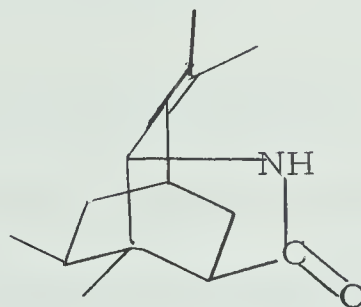
component into a methyl ester. The infrared spectrum of the material thus obtained showed bands at 1700 cm^{-1} (strong), 1720 cm^{-1} (strong), 3220 cm^{-1} (broad), 3440 cm^{-1} (medium, sharp). The band at 1720 cm^{-1} can be assigned to carbomethoxy group(s). The other three bands suggested the possible presence of a lactam function. The material obtained from treatment with ethereal diazomethane was subjected to chromatography on silica gel, and furnished a crystalline compound in ca. 15% yield. Structure 42 is assigned to this compound on the basis of the following considerations.



Elemental analysis of a recrystallized (m.p. $237-238^{\circ}\text{C}$) decomposition, MeOH) sample was consistent with the molecular formula $\text{C}_{24}\text{H}_{35}\text{NO}_3$ (MW 385). The C-1 ester group was indicated by a strong band at 1705 cm^{-1} in the infrared spectrum (nujol) and the lactam function was characterized by bands at 1690 cm^{-1} (strong $\begin{array}{c} \diagup \text{N}-\text{C}=\text{O} \\ \diagdown \text{H} \end{array}$) and 3360 cm^{-1} (N-H stretching mode). The n.m.r. spectrum shows signals at $\tau 9.21$ and $\tau 8.85$ assignable to the C-12 and C-1 methyl groups respectively. The methyl groups on C-18 resonate at $\tau 8.33$ and $\tau 8.18$.

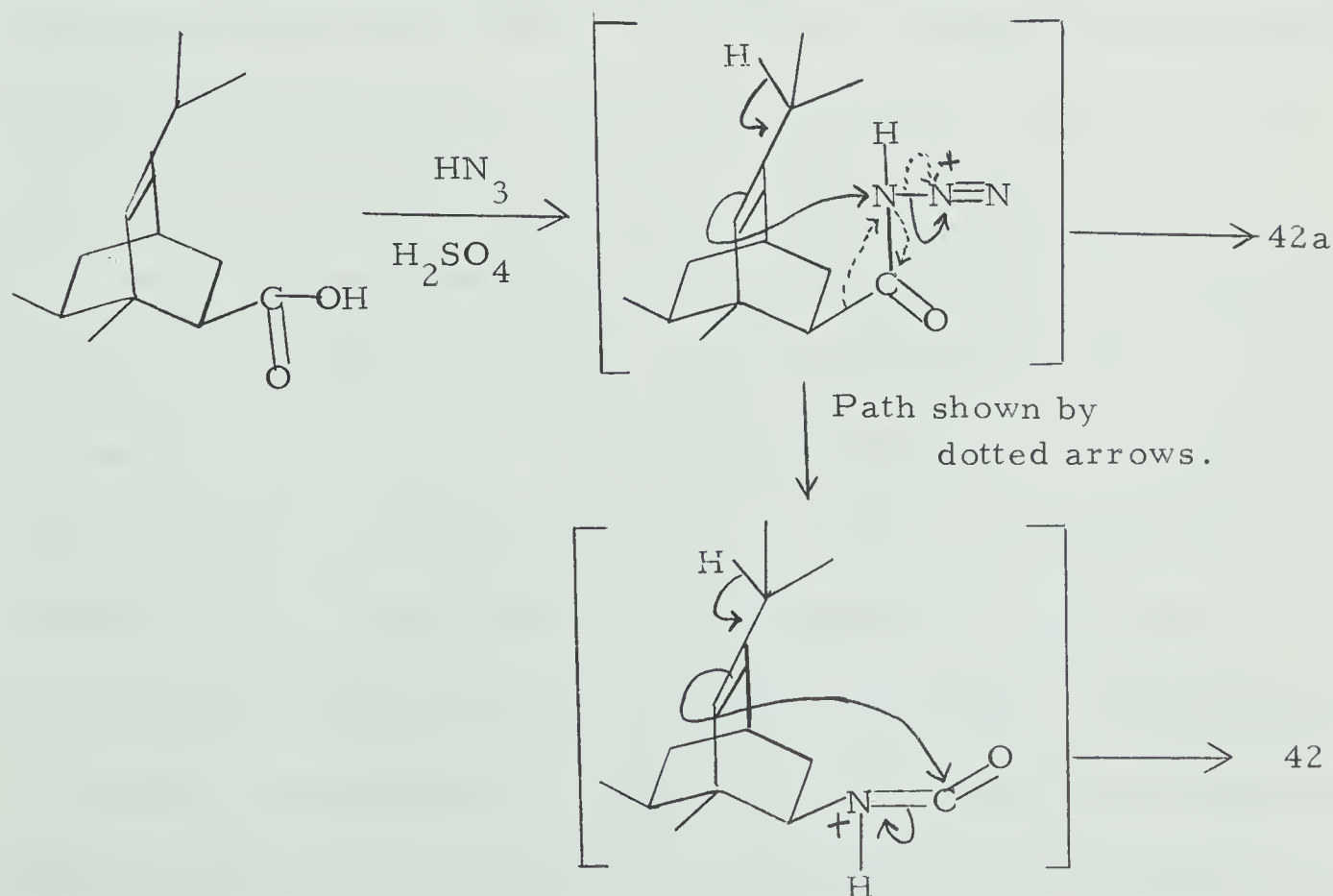
The C-1 carbomethoxy group is indicated by a three-proton singlet at τ 6.34 and the proton on nitrogen by a broad signal at τ 3.86. Three protons appear in the region τ 7.25-6.8. Two of these can be tentatively assigned to the protons on C-8 and C-22 but their exact assignment is not possible.

It should be pointed out that these data can also be rationalized in terms of an alternate structure indicated by 42a. Possible modes



42a

of formation of 42 and the isomeric compound represented by structure 42a are indicated below.



For the formation of 42, loss of nitrogen from the protonated intermediate azide and subsequent rearrangement to isocyanate are necessary. The isomeric compound 42a can arise if attack on the double bond occurs before rearrangement to isocyanate takes place. In order to confirm that the structure proposed for the lactam is as shown in 42 chemical degradations which would distinguish between the two alternatives 42 and 42a were undertaken.

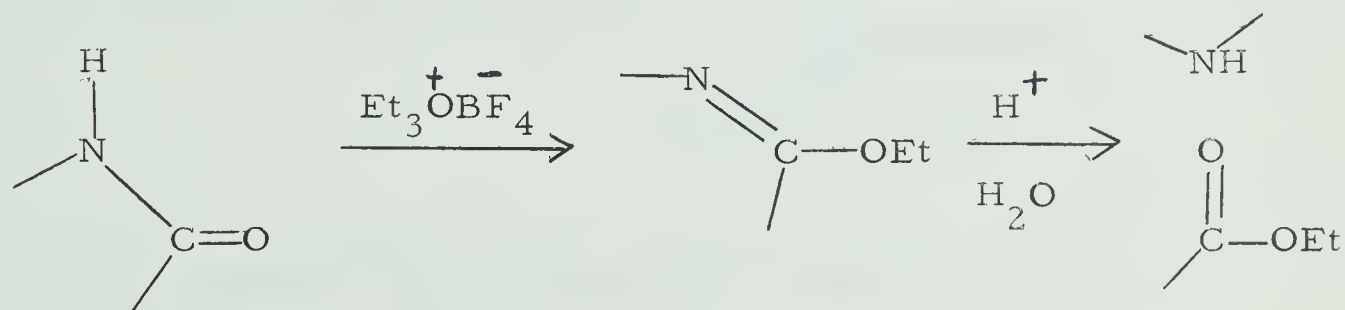
i) Opening of the Lactam by Acid Hydrolysis.

The first of the attempted chemical degradations involved opening of the lactam ring by hydrolysis with concentrated hydrochloric acid. This was undertaken in view of the fact that the carboxyl group (on C-8) that would be generated by hydrolysis might be induced to decarboxylate to produce amine 29 ($R = CH_3$ or H). Thermal decarboxylation³⁶ of β, γ unsaturated acids is a well-known reaction. Lactam 42 was subjected to treatment with refluxing constant boiling hydrochloric acid, which apparently resulted in the formation of an amine hydrochloride. This latter substance presumably had two carboxylic groups; one on C-1 and the other on C-8. The amine hydrochloride was difficult to handle because of solubility problems. In order to overcome this difficulty it was treated with ethereal diazomethane in the hope that the resulting ester might be easier to isolate in pure form. This afforded a crystalline compound which appeared to be a lactam from the infrared spectrum (1685 cm^{-1} , 3440 cm^{-1}). Comparison of this substance with

lactam 42 (m.p. , IR , NMR) however revealed that the two compounds were not identical. The nature of this product was not determined. Since this approach to the opening of lactam 42 and the subsequent decarboxylation did not succeed attention was turned to an alternative method of cleaving the lactam.

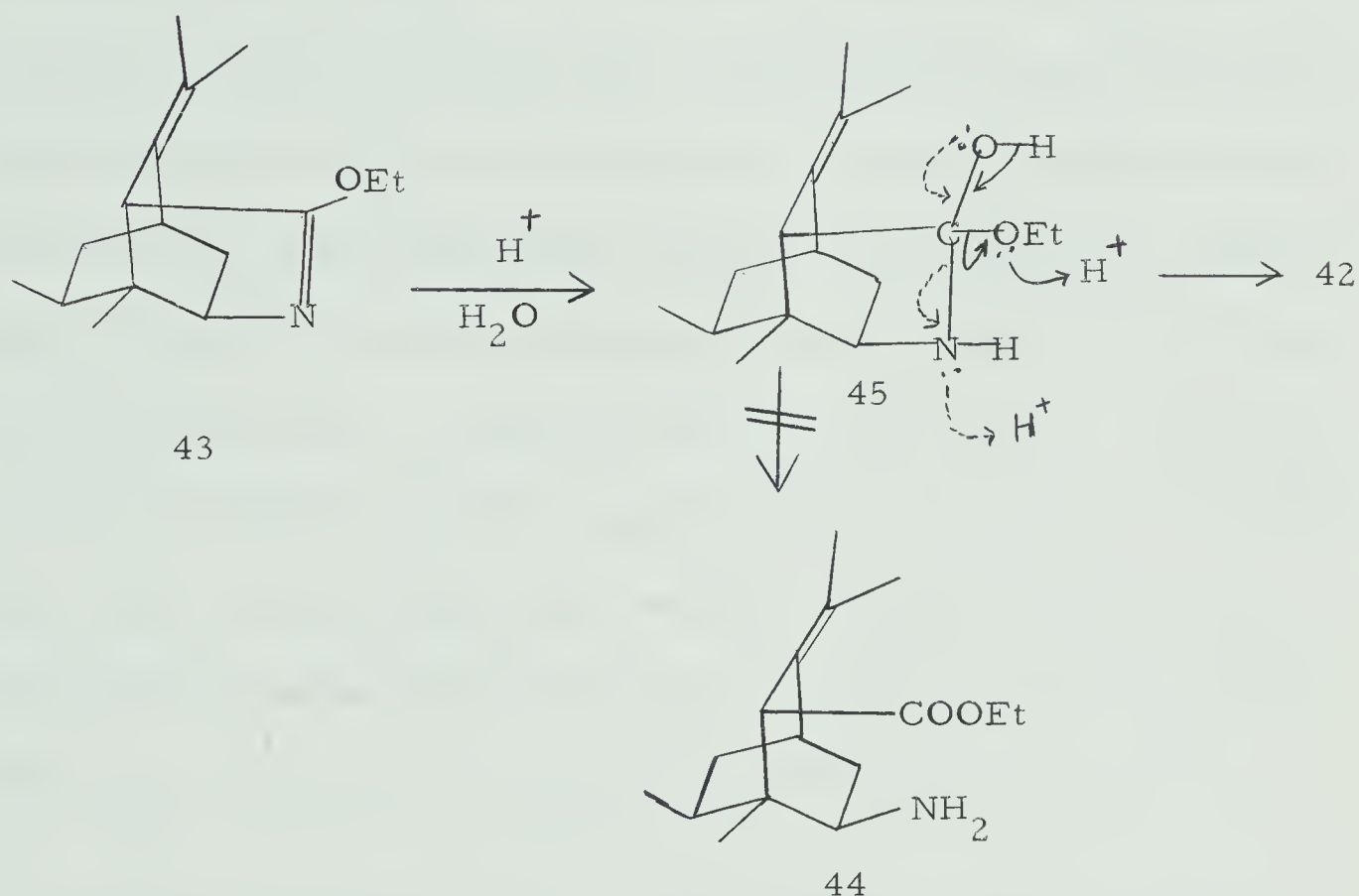
ii) Attempted Cleavage of the Lactam Ring via the Iminoether.

This approach was suggested by the work of Eschenmoser^{37a} and of Muxfeldt^{37b}. These authors have employed triethyloxonium fluoroborate in the hydrolysis of amides. The product of the reaction between an amide and triethyloxonium fluoroborate is an iminoether which is subsequently hydrolysed to an amino ester as shown.



Following this procedure the lactam 42 (in CH_2Cl_2) was treated with an excess of triethyloxonium fluoroborate. The product obtained from this reaction was identified as the iminoether 43 by means of the infra-red (strong band at 1640 cm^{-1} $\text{C}=\text{N}$) and the n.m.r. spectra ($-\text{OCH}_2\text{CH}_3$; a quartet at $\tau 6.0$ for CH_2 and a triplet at $\tau 8.8$ for CH_3 , $J = 7\text{ c.p.s.}$). Attempts to obtain compound 44 by hydrolysis of iminoether 43 with either aqueous acetic acid or sulfuric acid-dioxane were not successful. In both cases lactam 42 was recovered. It

appears that the intermediate 45 which results from acid catalyzed hydration of 43 reverts to lactam as shown (boldface arrows) rather than undergoing ring cleavage (dotted arrows).



iii) Formation of Lactam 42 from Isocyanate 47.

Confirmation of the structure proposed for lactam 42 was finally achieved by its preparation from isocyanate 47. This latter compound was obtained from adduct 31 ($\text{R} = \text{CH}_3$) in the course of an attempted Curtius reaction (for details see the next section). A chloroform solution of isocyanate 47 was treated with concentrated sulfuric acid for a short period and then the reaction mixture was subjected to work-up as in the Schmidt reaction. The neutral product obtained was subjected to chromatography on silica gel and a crystalline substance

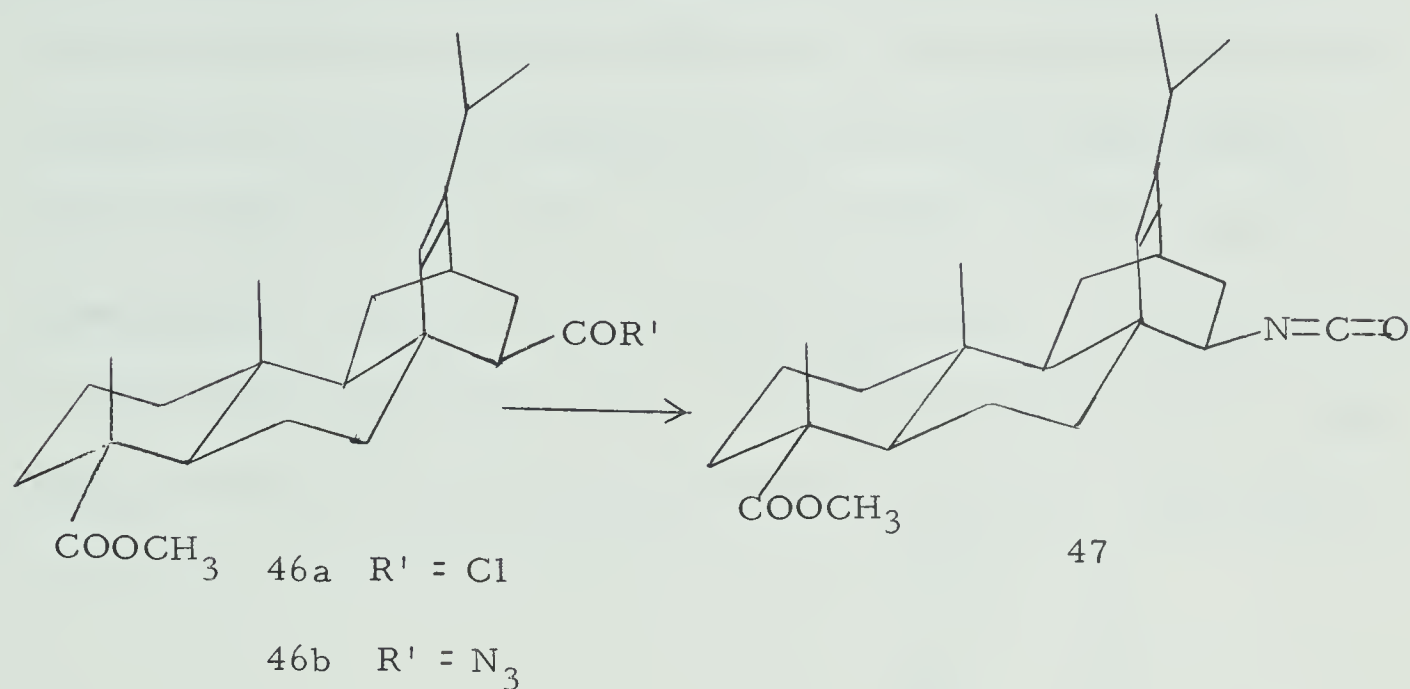
was obtained in ca. 13% yield. This crystalline substance was identical with lactam 42. Since in the isocyanate 47 the nitrogen atom is attached to C-22 it follows that in lactam 42 also the nitrogen atom must be attached to C-22. This fact rules out the alternative structure 42a in which C-8 bears a nitrogen atom. Subsequently a more convenient method for conversion of isocyanate 47 to lactam 42 was discovered. This involved simply passing the isocyanate over silica gel. Participation of the \triangle^{7-8} double bond in the reaction of adduct 31 ($R = CH_3$) with lead tetraacetate was pointed out in the last section. Formation of lactam 42 furnishes another example of the involvement of the \triangle^{7-8} double bond in an intramolecular reaction. It may be mentioned in passing that lactam ring formation has been observed in electrophilic attack of an isocyanate on aromatic rings^{38a} and on an enol^{38b}.

b) Attempted Transformation of Adduct 31 ($R = CH_3$) to Amine 29 ($R = CH_3$) by the Curtius reaction.

Since the Schmidt reaction did not prove satisfactory for the conversion of adduct 31 ($R = CH_3$) to amine 29 ($R = CH_3$) the Curtius reaction was investigated. As pointed out before, this reaction was used by Goering in the synthesis of compound 27. In view of the structural similarity between the precursor acid of compound 27 and adduct 31 ($R = CH_3$) it was felt that the Curtius reaction might be more effective in the preparation of amine 29 ($R = CH_3$). It soon became

apparent that this method also was not completely satisfactory.

Adduct 31 ($R = CH_3$) was converted into acid chloride 46a by

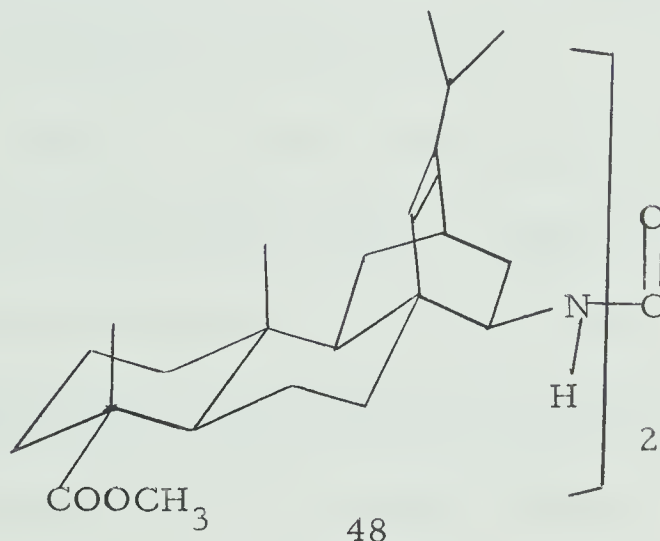


treatment with excess thionyl chloride in benzene. This reaction appeared to be quantitative as judged by the infrared spectrum (1800 cm^{-1} , $-\overset{\text{O}}{\parallel}{C}-Cl$, no band for $COOH$) of the product. Transformation of acid chloride 46a into acyl azide 46b was achieved by treating an acetone solution of the former with an aqueous solution of sodium azide. Actually, the product obtained from this reaction was a mixture of acyl azide and isocyanate as shown by the infrared spectrum (2260 cm^{-1} for $N=C=O$ and 2140 cm^{-1} for CON_3). When this mixture was heated under reflux in benzene for 3-4 hours complete transformation of the azide to isocyanate 47 was effected. The isocyanate was obtained as a brown foam (IR 2260 cm^{-1} , v. strong). This material was used without further purification in the next step. Initially isocyanate 47 was subjected to

alkaline hydrolysis which gave a basic product in poor (2%) yield.

The nonbasic product of this reaction ($>90\%$) showed bands at 1500 cm^{-1} , 1670 cm^{-1} , 1720 cm^{-1} , and 3440 cm^{-1} (w) in the infrared.

Chromatography of the nonbasic material on silica gel afforded in overall 5% yield a crystalline compound (m.p. $158-160^{\circ}$) which showed bands at 1500 cm^{-1} (m), 1670 cm^{-1} (s) and 3440 cm^{-1} (m) besides a strong band at 1720 cm^{-1} in the infrared spectrum. A possible structure for this compound is shown in 48. Compounds of this type (i.e., symureas) are known³⁹ to be formed in Curtius reactions. Hydrolysis of



isocyanate 47 in acidic medium (DME/HCl) afforded a basic product in 15-20% and a nonbasic product in 60-65% yield. The latter, on crystallization from methanol afforded lactam 42 in ca. 8% overall yield.

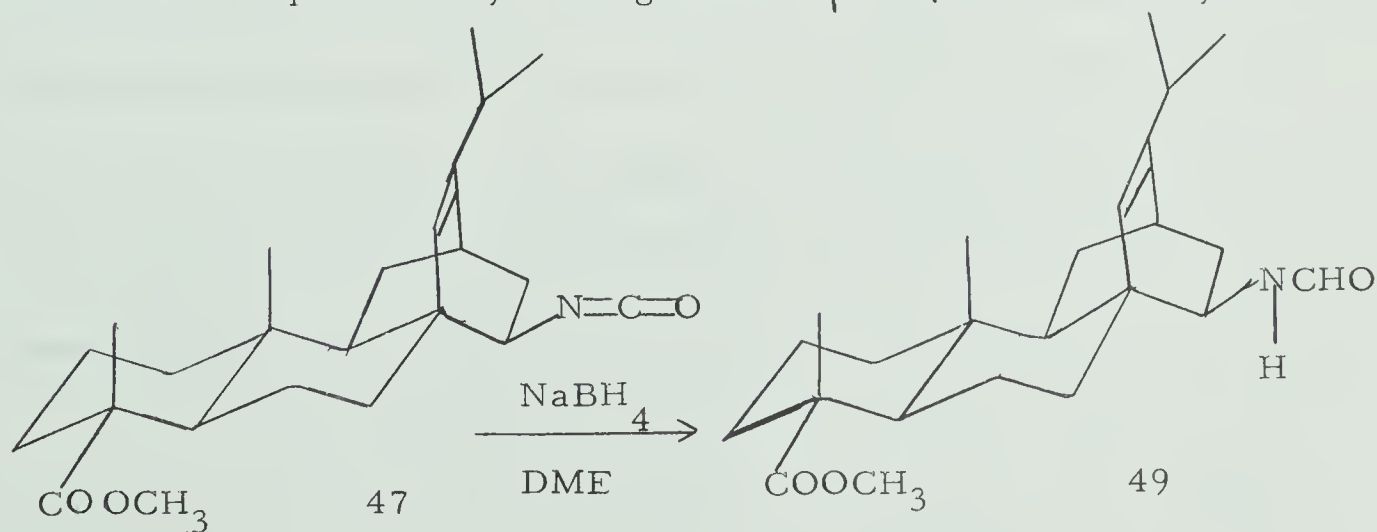
Since yields of basic product from the Curtius reaction were poor a different approach to the preparation of amine 29 ($R = \text{CH}_3$) was adopted.

c) Preparation of Amine 29 ($R = \text{CH}_3$) from Isocyanate 47 by Hydride Reduction-Hydrolysis Sequence.

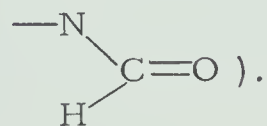
Preparation of amine 29 ($R = \text{CH}_3$) in satisfactory yields was

finally accomplished by a method which involved reduction of isocyanate 47 to the N-formyl compound 49 and subsequent hydrolysis of the latter compound. Isocyanates are known⁴⁰ to yield N-methyl compounds on reduction with lithium aluminum hydride. This transformation of isocyanate to N-methyl compound presumably occurs via an intermediate N-formyl derivative. It was felt that by using a weaker reducing agent such as sodium borohydride it might be possible to stop the reduction at the N-formyl stage. Acid hydrolysis of the N-formyl compound would then lead to a primary amine. This sequence was used successfully in the preparation of amine 29.

Reduction of isocyanate 47 was effected by treatment with excess sodium borohydride in dimethoxyethane (DME). This reaction furnished in quantitative yield the compound 49 as a white foam. The N-formyl group of 49 was identified in the infrared spectrum by the bands at 1680 cm^{-1} (v. strong), 3400 cm^{-1} (w, broad), 3435 cm^{-1} (m) and in the n.m.r. spectrum by the signals at $\tau 4.5$ (centre of very broad



absorption, N-H) and $\tau 1.96$ (singlet,

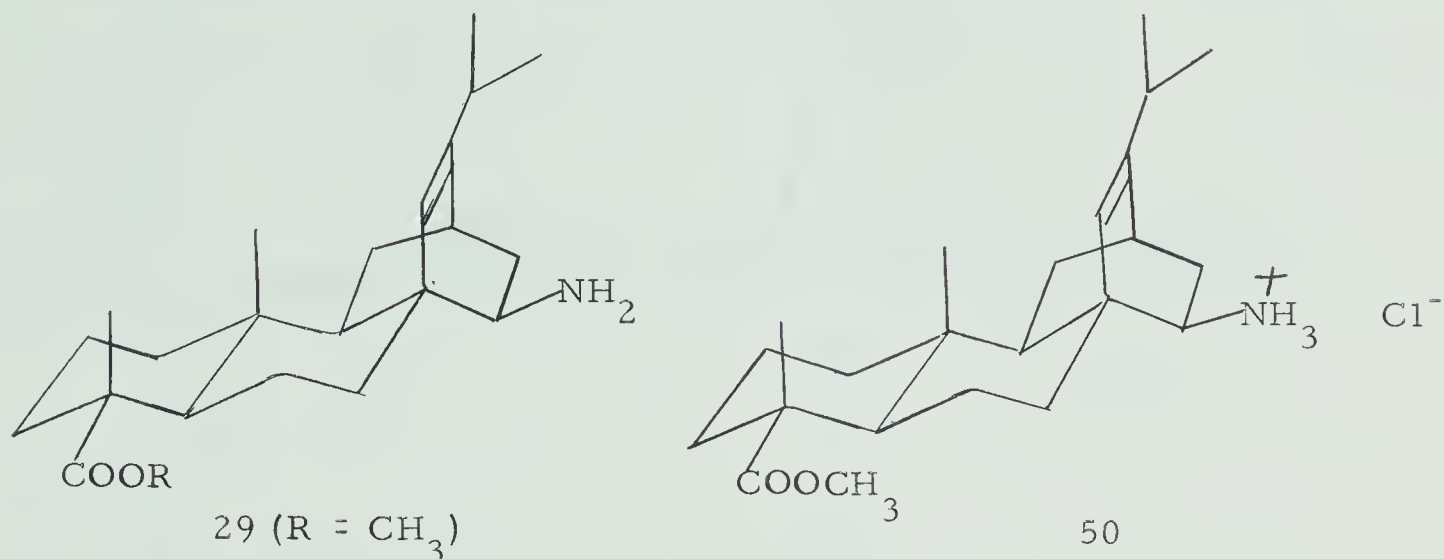


Hydrolysis of compound 49 in refluxing ethanolic hydrochloric acid (3:1) afforded amine 29 ($R = CH_3$) as a viscous oil in ca. 75% overall yield.

A pure sample of amine 29 ($R = CH_3$) was prepared via its crystalline hydrochloride 50 which was obtained by passing dry HCl into an ether solution of the base. In agreement with the molecular formula $C_{23}H_{37}NO_2$ (MW 359) the amine 29 ($R = CH_3$) showed a molecular ion at m/e 359 in the mass spectrum and gave a satisfactory elemental analysis. Similar to that of ester 34, the mass spectrum of amine 29 ($R = CH_3$) shows a strong peak at m/e 316 arising by loss of a vinylamine moiety from the molecular ion via a retro Diels-Alder reaction.

The infrared spectrum of amine 29 ($R = CH_3$) shows bands at 1660 cm^{-1} (w, $C=C$), 1720 cm^{-1} (s, $C_1-COOCH_3$) and $3200-3500\text{ cm}^{-1}$ (v.w., $-NH_2$). The n.m.r. spectrum is consistent with the structure 29 ($R = CH_3$). Thus, the C-12 methyl group (shielded by the \triangle^{7-8} double bond) appears at τ 9.38 and the C-1 methyl resonates at τ 8.85. The isopropyl group on C-8 is characterized by a 6-proton doublet ($J = 7\text{ c.p.s.}$) at τ 8.95. The signals at τ 6.35 (3H, s) and τ 4.74 (1H, s) are assigned to the C-1 carbomethoxy group and the proton on C-8 respectively.

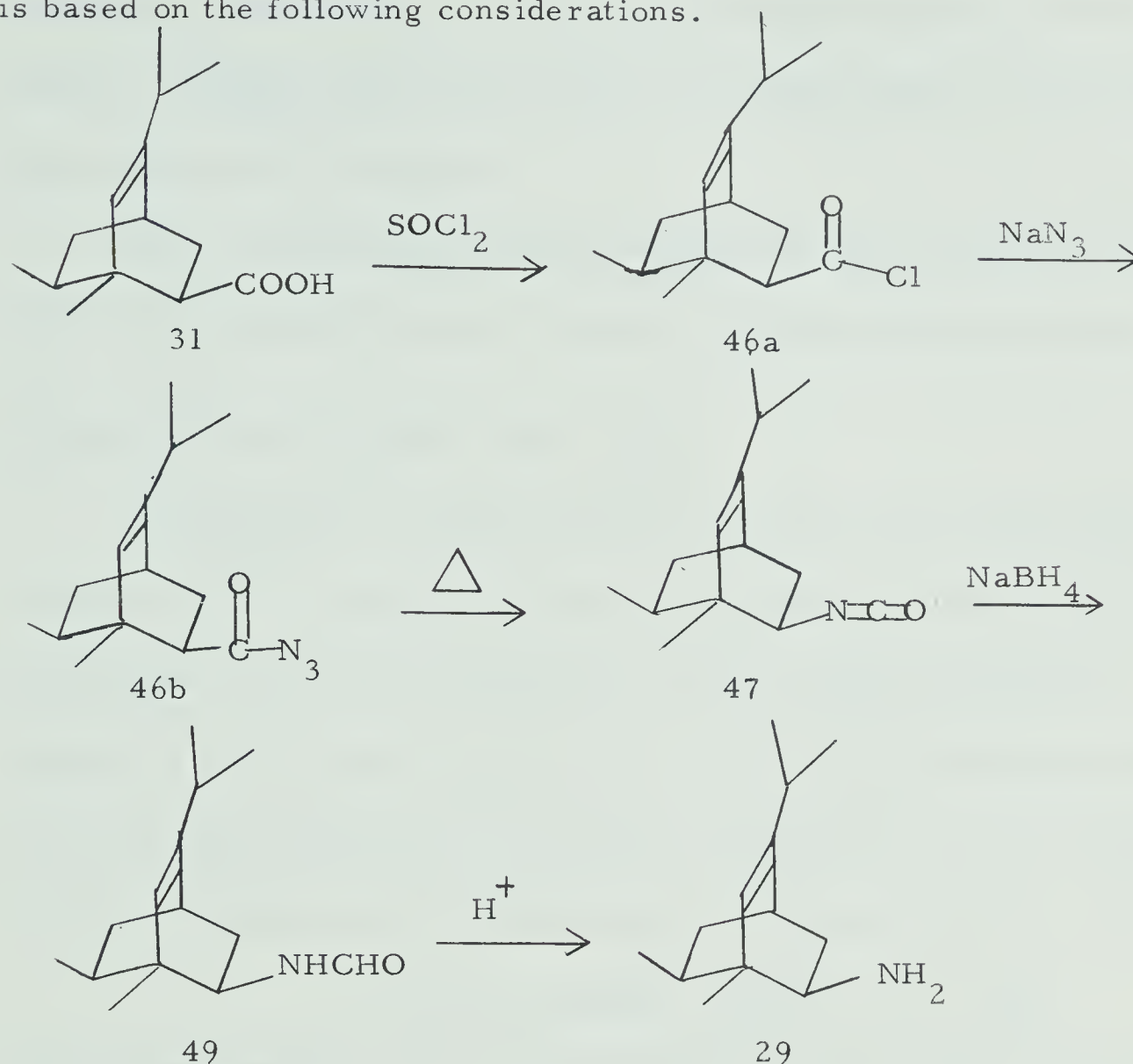
Spectral properties of the amine hydrochloride* (50) are in agreement with the proposed formulation. As mentioned before, amine



29 forms a crystalline hydrochloride (m.p. 210-214^o, crystallized from methyl acetate) when an ethereal solution is treated with hydrogen chloride. The salt, especially when impure, is soluble in ether and a pure crystalline sample dissolves in chloroform with as much facility as it does in water. The infrared spectrum of amine hydrochloride 50 shows bands at 1500 cm⁻¹ (m), 1580 cm⁻¹ (m), and 3000-3100 cm⁻¹ (sh.) attributable to the NH₃⁺ group, the presence of which is also indicated by a broad, 3-proton signal at τ 2.03 in the n.m.r. spectrum. Other n.m.r. data are consistent with the structure 50.

* The amino 29 bears some structural similarity to 1-aminoadamantane, which has enjoyed some success as an antiviral agent, and was therefore selected for physiological testing. Although its effectiveness as an antiviral has yet to be determined, preliminary tests (carried out by Ayerst Laboratories, Montreal) indicate that 29 has significant monoamine oxidase inhibitory activity. It will be noted that 29 bears some structural similarity to the powerful MAO inhibitor 2-phenylcyclopropylamine (tranylcypromine).

The assignment of the β configuration to the amino group in 29 is based on the following considerations.



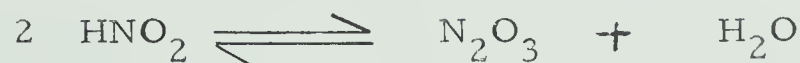
As discussed in the early part of this thesis, the endo configuration of the C-22 carboxyl group in the adduct 31 has been established. A change in the configuration of the C-22 function in 46a, 46b and 47 is not expected since formation of the first two compounds does not involve the C-22 as a reaction site and the rearrangement of an acyl azide to isocyanate as in 46b and 47 is known³⁹ to occur with retention in configuration. Formation of lactam 42 from isocyanate 47 confirms that the C-22 $\text{N}=\text{C}=\text{O}$ group is β -oriented. Conversion of isocyanate

47 by reduction with NaBH_4 to the N-formyl compound 49 and acid hydrolysis of the latter are not expected to affect the stereochemistry at C-22. The β configuration of the C-22 amino group in 29 can therefore be taken as established.

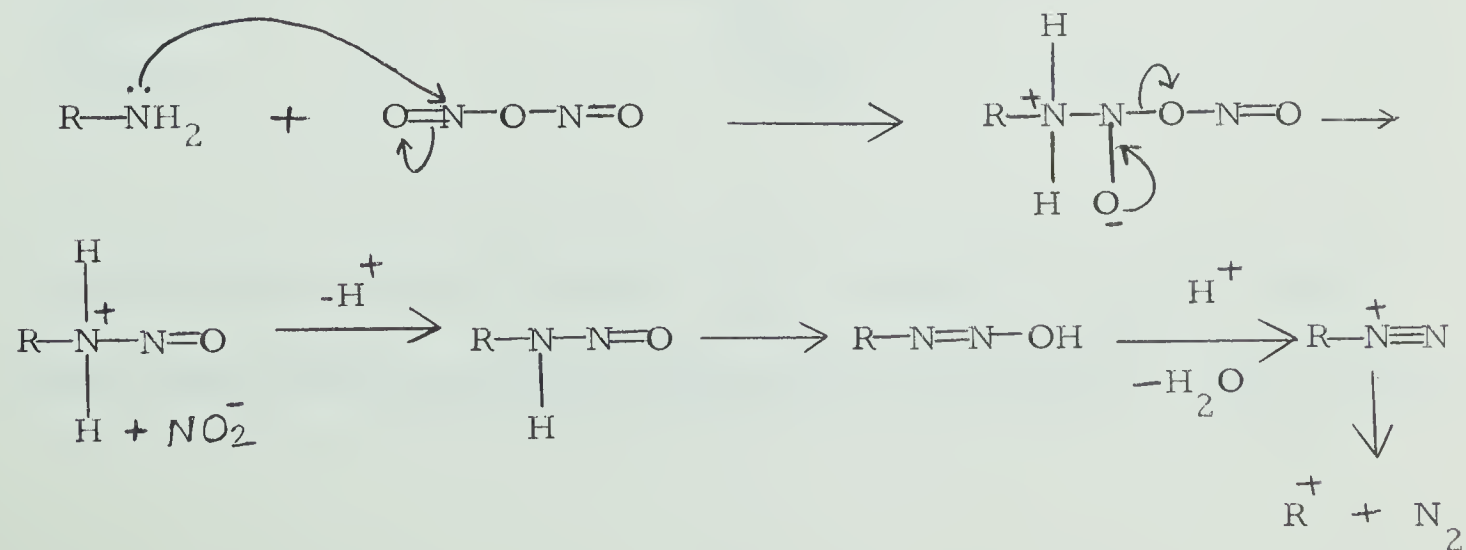
With a satisfactory method available for the synthesis of amine 29 ($\text{R} = \text{CH}_3$) attention was now turned to the deamination reaction.

DEAMINATION OF AMINE 29 ($\text{R} = \text{CH}_3$).

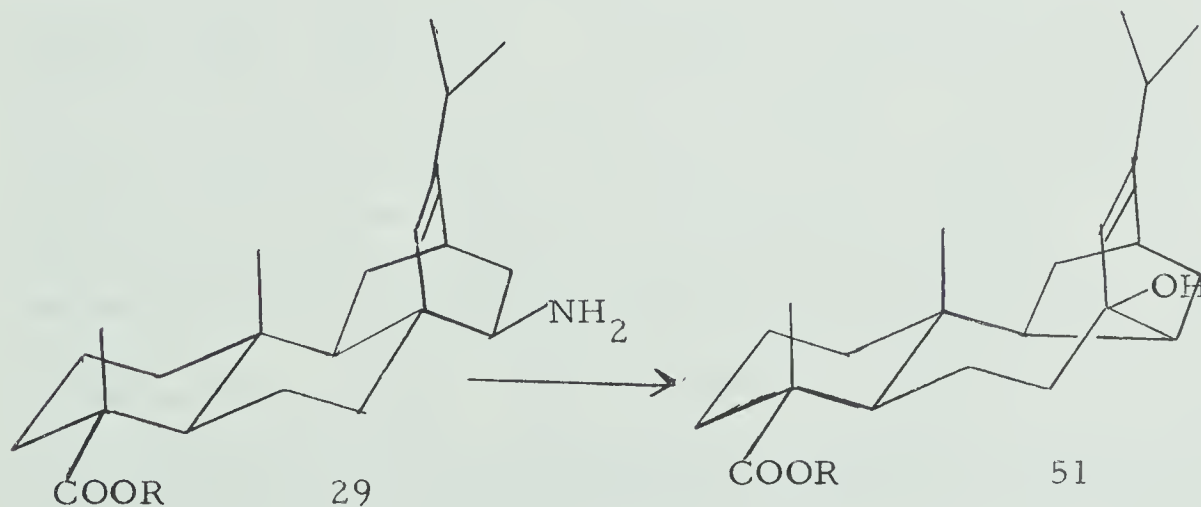
Deamination of aliphatic primary amines may be effected in several ways⁴¹. The most common among these involves treatment of an amine with nitrous acid which is usually produced in situ by reaction of sodium nitrite and an acid. The active nitrosating species in nitrous acid deamination⁴² has been recognized as nitrous anhydride present in equilibrium with nitrous acid. Nitrous anhydride reacts



with primary amines to produce carbonium ions from which the products of the deamination reaction are believed to be derived. The sequence by which carbonium ions are formed from primary amines is given below.



Although the intermediacy of carbonium ions in deamination usually leads to the formation of a variety of products the reaction can be useful in bringing about stereospecific rearrangements as illustrated by the example^{21b} involving amine 29. The usual procedure used in nitrous acid deaminations involves addition of excess sodium nitrite to an acidic solution of the amine or of the amine salt. Hydrochloric acid, aqueous acetic acid and glacial acetic acid are among the commonly used acids. Perchloric acid and fluoboric acid, which have weakly nucleophilic anions, have also been used. Following the procedures of Wildman^{21a} and Goering^{21b} amine 29 ($R = CH_3$) was subjected to deamination in aqueous hydrochloric acid, aqueous acetic acid, and glacial acetic acid with the expectation that an analogous alcohol (51) (or a derivative) would be obtained.



In practice deamination of 29 ($R = CH_3$) resulted in a complex mixture from which several unexpected compounds were isolated. Their isolation

and characterization will now be discussed.

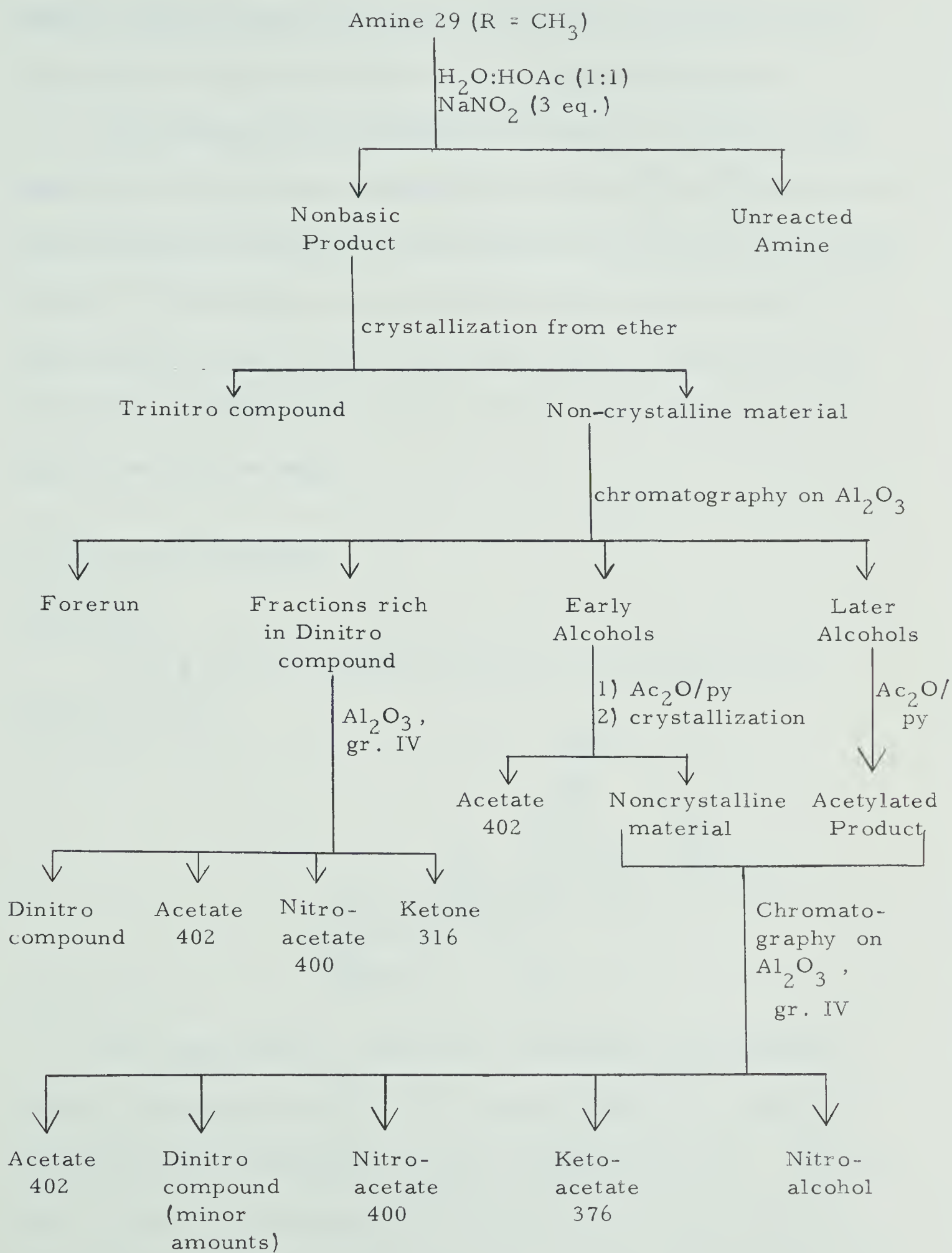
a) Isolation of Products.

Initially, small scale deaminations of 29 ($R = CH_3$) were carried out. These involved reaction of sodium nitrite with (1) an aqueous fluoboric acid solution of amine 29 and (2) an aqueous solution of amine hydrochloride 50 containing a slight excess of HCl. In each case the nonbasic product isolated from the reaction was a complex mixture of several components as revealed by their thin layer chromatographic behaviour and the spectral properties. Chromatographic separation employing alumina and silica gel columns were not successful. Attention was therefore turned to deamination in glacial acetic acid. When a solution of the amine hydrochloride 50 in acetic acid was treated with an excess of sodium nitrite, nonbasic material was obtained in ca. 70% yield. A colorless crystalline substance, which will be referred to as the "trinitro compound", separated (ca. 12% yield) from the ether solution of the nonbasic product. The trinitro compound shows strong absorption in the $1540-1570\text{ cm}^{-1}$ region of the infrared spectrum. Early attempts to separate by chromatography the components in the noncrystalline material remaining after isolation of the trinitro compound were not successful. Later, a yellow crystalline substance, referred to as the "dinitro compound", was isolated in ca. 3% overall yield. The isolation of this compound was successful only after seed crystals of the dinitro compound became available from

the aqueous acetic acid deamination (see below).

Although the trinitro compound was the first pure product isolated from the deamination of amine 29 ($R = CH_3$), elucidation of its structure was not undertaken for some time since it appeared to be a highly nitrated (3 nitro groups) substance. Isolation of a product of this type appeared to have no precedent in nitrous acid deaminations reported in the literature.

With a view to obtaining the more usual type of product, i.e. alcohols, acetates, etc., experiments involving deamination of amine 29 ($R = CH_3$) in aqueous acetic acid were initiated. The nonbasic products obtained from these experiments showed absorption at 1540-1560 cm^{-1} (strong) and 3400-3600 cm^{-1} (weak) in the infrared spectrum indicating that both nitrated and hydroxylic products were formed in the deamination reaction. Initial attempts to isolate the components of the deaminated product were not successful. However, after considerable experimentation a procedure involving repeated chromatography was developed for the separation of several compounds from the deamination product. The chart on the next page diagrams this procedure. The following compounds were isolated: 1) Trinitro compound (2-3%); 2) Dinitro compound (6-8%); 3) Acetate 402 (5-6%); 4) Nitroacetate 400 (3-4%); 5) Ketoacetate 376 (\approx 2%); 6) Ketone 316 (2-3%); 7) Nitroalcohol (5-6%). The figures in brackets indicate approximate overall yields based on the nonbasic product used in the chromatography; the



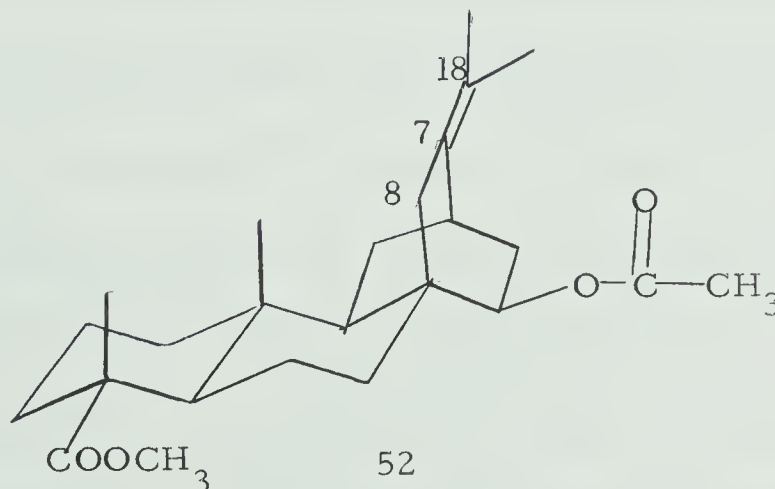
numbers following the trivial names correspond to the highest mass ions produced in the mass spectra of the compounds concerned.

The acetates were investigated first since it was felt that they might have the desired rearranged skeleton (bicyclo[3.2.1]octane system). The investigation revealed that the acetates in fact have an unrearranged skeleton. Interestingly enough compounds other than the acetates were found to possess the bicyclo[3.2.1]octane system. Discussion of the structural elucidation of the acetates and the other compounds will be found in the next few pages.

b). Structural Elucidation

Acetate 402

Acetate 402 was assigned structure 52 on the basis of the following evidence.



The compound (m.p. 145-146^o, crystallized from methanol) showed a molecular ion at m/e 402 in the mass spectrum, which is in agreement with the molecular formula C₂₅H₃₈O₄ (MW 402). The mass spectrum shows a strong peak at m/e 342 which presumably arises by loss of acetic acid from the molecular ion. This fact is suggestive of

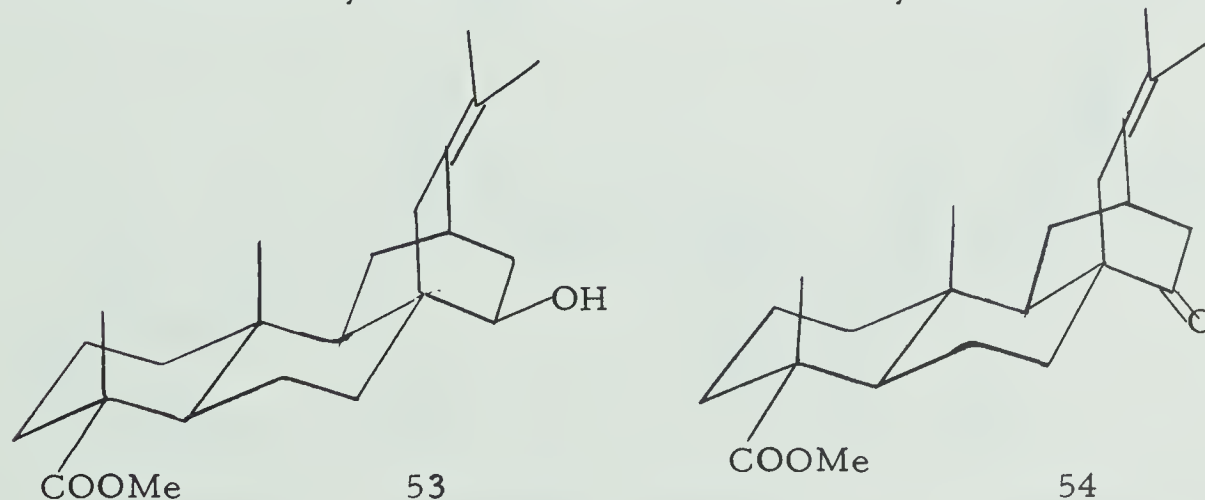
the presence of an acetoxy group. The presence of this grouping is also indicated by a signal at $\tau 8.02$ (3H, singlet $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$) in the n.m.r. spectrum and a band at 1370 cm^{-1} (medium, $\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$, $\int s$) in the infrared spectrum. The carbonyl stretching vibrations of the acetoxy group and the carbomethoxy group overlap to give a strong band at 1730 cm^{-1} in the infrared spectrum of acetate 402. The ester group gives rise to a three proton singlet at $\tau 6.37$ in the n.m.r. spectrum. In agreement with the proposed structure the n.m.r. spectrum shows two methyl groups attached to saturated carbon atoms. The signal at $\tau 9.16$ (shielded by the \triangle^{7-18} double bond) is attributed to the C-12 methyl group and the one at $\tau 8.85$ is assigned to the C-1 methyl group. The methyl groups on C-18 appear as broad singlets at $\tau 8.46$ and $\tau 8.37$. Spin-decoupling experiments indicated this broadening is due to a proton or protons resonating at about $\tau 7.8$. Evidently this is a case of homoallylic coupling. The C-22 proton, geminal to the acetoxy group, appears at $\tau 5.48$ as a broad doublet. Under high resolution the broad doublet could be seen to be an octet with coupling constants of ≈ 9 c.p.s., ≈ 3 c.p.s. and ≈ 1.5 c.p.s. The coupling constants of 9 and 3 c.p.s. are consistent with the observed⁴³ coupling constants for vicinal protons in bicyclo $[\bar{2} \cdot 2 \cdot 2]$ octane systems. The coupling constant of 1.5 c.p.s. must be associated with a long range coupling presumably to the anti proton at C-8.

More evidence in support of this proposed structure for acetate

402 was sought by chemical degradation.

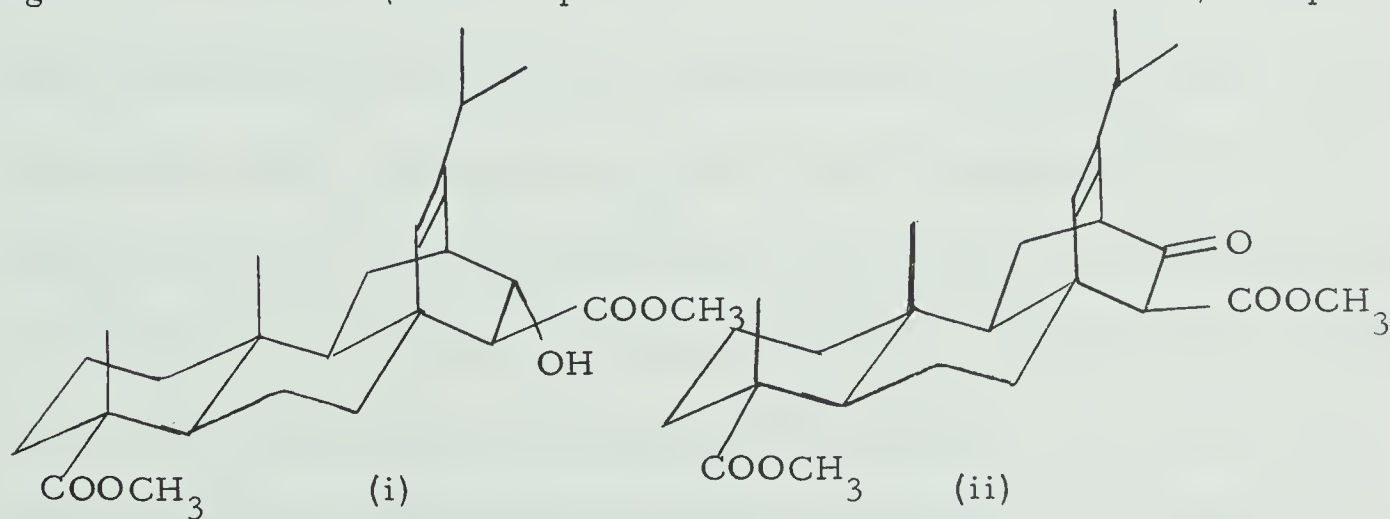
Acetate 402 was subjected to pyrolysis (300° , 35 mm) in the hope that the olefin that might result by elimination of acetic acid would furnish more information about the environment of the C-22 acetoxy group. Unchanged acetate 402 was obtained under these conditions.

In another approach acetate 402 was subjected to Zemplen methanolysis to afford alcohol 53. This latter substance could not be induced to crystallize. The spectroscopic properties of the alcohol are consistent with structure 53. The infrared spectrum of 53 contains bands at 1720 cm^{-1} (COOMe) and 3600 cm^{-1} (-OH) and the n.m.r. spectrum displays signals at τ 9.14 (3H, singlet, C-12 methyl), τ 8.84 (3H, singlet, C-1 methyl), τ 8.46 and τ 8.37 (C-18 methyls), τ 6.58 (1H, C-22 H, broad doublet) and τ 6.37 (3H, singlet C₁-COOCH₃). Alcohol 53 was oxidized by Jones' method⁴⁴ to the oily ketone 54. This compound



showed a molecular ion at m/e 358, which is consistent with the molecular formula $C_{23}H_{34}O_3$ (MW 358). The infrared spectrum of ketone 54 shows a broad band at 1720 cm^{-1} caused by overlapping of the

absorptions due to the carbomethoxy and the ketonic functions and shows no hydroxyl absorption. The presence of a keto group is supported by the appearance of a weak band at 1410 cm^{-1} attributable to the scissoring mode of an active methylene group ($-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{CH}_2$). The n.m.r. spectrum of ketone 54 shows a three proton singlet at $\tau 9.06$ assignable to the C-12 methyl group. Compared to the chemical shifts of the C-12 methyls in acetate 402 and the alcohol 53 this is lower by ca. 0.1 ppm. We attribute this lower chemical shift of the C-12 methyl in 54 to the deshielding effect of $\text{>}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}_{22}\text{O}$ function. A similar difference in the chemical shifts of the C-12 methyl is observed between the acetate 76b and the ketone 80a (see next chapter). A deshielding effect on the C-12 methyl group of (ii) has been reported by McDonald²⁹. Greater deshielding in the ketone 54 (with respect to acetate 402 or alcohol 53) compared



Reported	C-12 Me	(i) $\tau 9.37$	(ii) $\tau 9.32$
----------	---------	-----------------	------------------

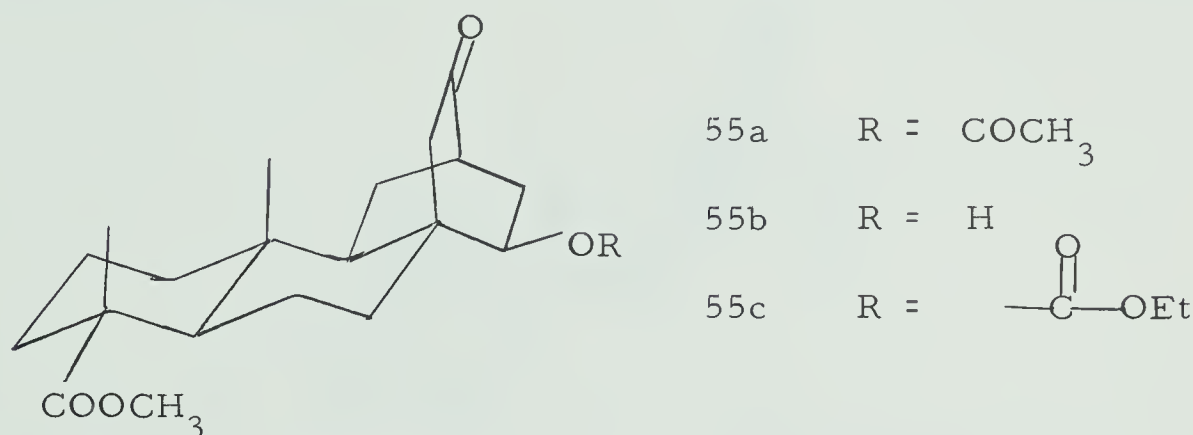
to that reported in compound (ii) supports the location of the ketone function at C-22 in the former compound.

More information about the environment of the C-22 carbonyl

function was sought by attempted deuteration (DCI-DOAc) of the C-21 methylene group. The product obtained from this reaction was intractable.

Confirmatory evidence for the structure proposed for acetate 402 came from its degradation to the known²⁰ ketoolefin 56.

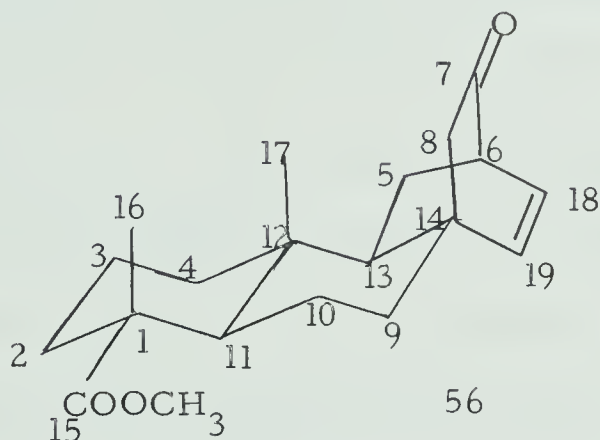
Ozonolysis of acetate 402 (ethyl acetate, H_2O_2 - H_2O work-up) afforded ketoacetate 55a (m.p. 217-222°) in ca. 55% yield. The mass



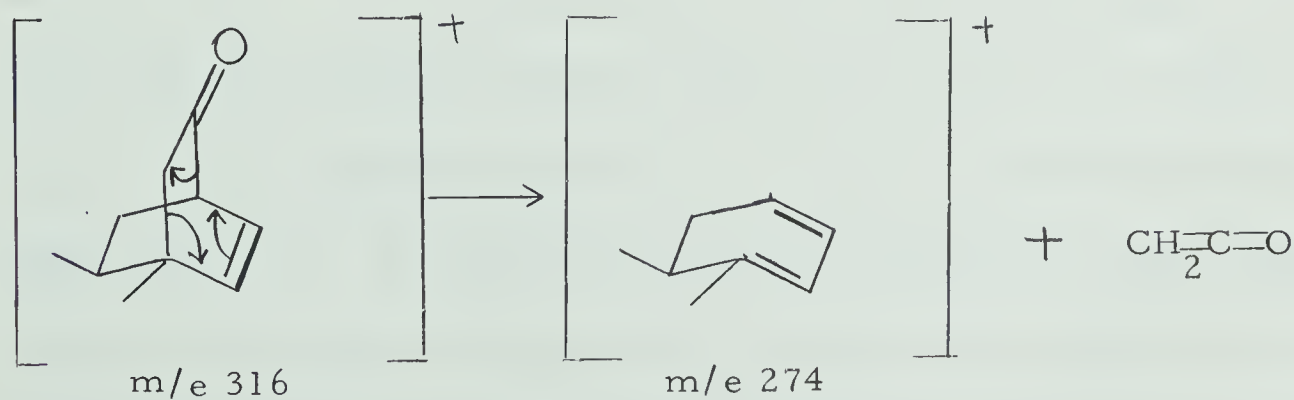
spectrum of compound 55a showed a parent peak at m/e 376. Exact mass measurement revealed its composition as $C_{22}H_{32}O_5$ (Calc. 376.2249, Found. 376.2247). The infrared spectrum of ketoacetate 55a contains bands at 1370 cm^{-1} (m, δ_s $O-\overset{O}{\parallel}C-CH_3$), 1405 cm^{-1} (w, scissoring mode of $-\overset{O}{\parallel}C-CH_2$) and 1720 cm^{-1} (broad and strong, $>C_7=O$ and $C_1-COOMe$). Loss of the isopropylidene group during ozonolysis is indicated by the n.m.r. spectrum which shows the absence of signals attributable to this group.

Compound 55a was converted into alcohol 55b by hydrolysis in refluxing methanolic potassium hydroxide. Attempts to dehydrate alcohol 55b to ketoolefin 56 by treatment of the former with phosphorous

oxychloride and pyridine did not succeed. The alcohol 55b was therefore converted to cathylate 55c by treatment with ethyl chloroformate⁴⁵ in pyridine. The yield of the cathylation product was quantitative. Cathylate 55c was pyrolyzed in a sealed tube (240-250^o) to afford a dark brown product which on sublimation furnished ketoolefin 56 in 30% over-all yield. Assignment of structure to the ketoolefin is based on the following considerations.

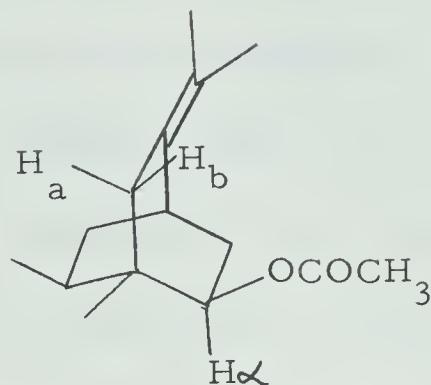


Ketoolefin 56 (m.p. 166-169^o, reported²⁰ 166-168^o) shows a molecular ion at m/e 316 which is consistent with the molecular formula C₂₀H₂₈O₃. The base peak at m/e 274 can be readily explained, on the basis of structure 56, as arising by a retro Diels-Alder reaction as shown below.



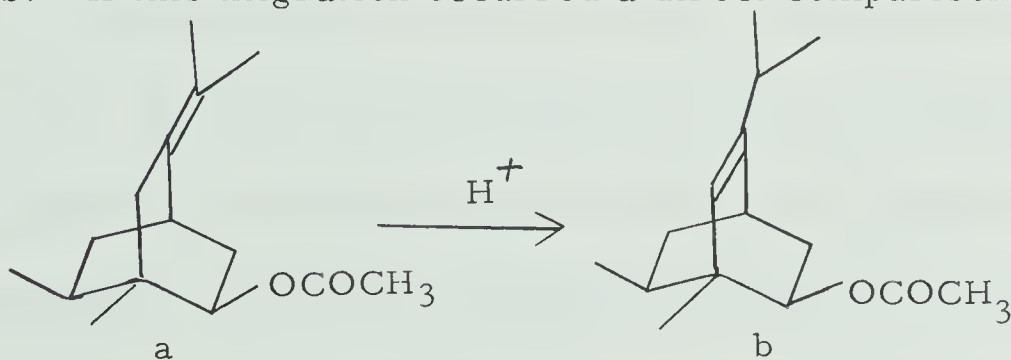
The infrared spectrum (CCl_4) shows bands at 1410 cm^{-1} (w, $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—CH}_2$), 1612 cm^{-1} ($\text{C}=\text{C}$), 1722 cm^{-1} ($\text{>C}\overset{\text{O}}{\parallel}\text{O}$ and $\text{C}_1\text{—COOMe}$); (KBr) 1244 cm^{-1} , 1614 cm^{-1} (sh), 1724 cm^{-1} (reported 1248 cm^{-1} , 1616 cm^{-1} , 1724 cm^{-1}). The n.m.r. spectrum is consistent with the structure 56. The methyl groups appear at $\tau 9.10$ (C-12 Me), $\tau 8.85$ (C-1 Me) and $\tau 6.35$ ($\text{C}_1\text{—}\overset{\text{O}}{\parallel}\text{C}\text{—O—Me}$). The C-19, C-18 and C-6 protons constitute an ABX system. The AB part of this system is observed ($\tau 4.02\text{--}3.78$) as a poorly resolved eight line pattern⁴⁶ from which J_{AB} is evaluated as 8 c.p.s. The reported²⁰ chemical shifts for the olefinic protons are $\tau 3.87$ (1H) and 3.95 (d, $J = 3$ c.p.s.). The discrepancy between the observed and the reported values may well be due to the difference in the conditions under which the spectra were determined (observed on Varian HR100; reported on Varian A-60). Our request for an authentic sample of 56 was not acknowledged.

The stereochemistry assigned to the C-22 acetoxy group of acetate 402 is not definitely established. Initially the β configuration for the former was assigned from a consideration of the n.m.r. spectrum of acetate 402. As mentioned before, the C-22 proton appears as an octet with the coupling constants of ≈ 9 c.p.s., ≈ 3 c.p.s. and ≈ 1.5 c.p.s.. The coupling constant of 1.5 c.p.s. is believed to be of the long range type. An attractive possibility for the long range coupling appears to be between the H_a and H_β protons which satisfy the required W arrangement⁴⁷. Spin-decoupling experiments undertaken to confirm



this long range coupling between the two protons were not successful since the chemical shifts between the C-21 protons and the C-8 protons are not sufficiently large.

Another approach to the determination of the configuration of the C-22 acetoxy group became feasible when the acetate 76b (see Chapter III) became available from other work. It was felt that the Δ^{7-18} double bond in acetate 402 might be induced to undergo acid catalyzed migration to the Δ^{7-8} position as indicated in part structures a and b. If this migration occurred a direct comparison between the



product (part structure b) thus obtained, and acetate 76b would reveal whether the C-22 acetoxy group in acetate 402 is β -oriented or not. With this purpose in mind acetate 402 was subjected to treatment (r.t. 48 hours) with acetic acid saturated with hydrogen chloride. The product obtained, showed a single spot on t.l.c. (silica gel) but the n.m.r.

spectrum indicated a mixture of more than two components. The spectrum was clean enough to permit recognition of signals at τ 9.37, τ 8.97 (d, $J = 6.5$ c.p.s.), τ 8.86, τ 8.07, τ 5.44 (broad) similar to those present in the n.m.r. spectrum of 76b. The signal at τ 8.07, which may be assigned to an acetoxyl group, favors the \nearrow orientation of this group (i.e. shielded by the double bond, see Chapter III). Attempts to isolate this compound in pure form were not successful.

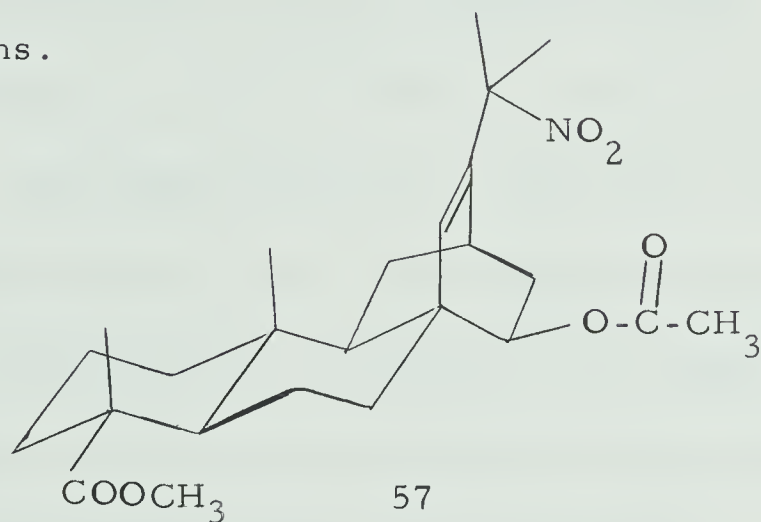
Ketoacetate 376

Ketoacetate 376 (m.p. $218-222^{\circ}$, crystallized from methanol) shows a molecular ion at m/e 376 in the mass spectrum. The occurrence of a compound of this molecular weight was difficult to explain on the basis of any structure derivable from amine 29 ($R = CH_3$) by a simple deamination process. The infrared spectrum of ketoacetate 376 shows bands at 1370 cm^{-1} (m), 1405 cm^{-1} (w), and 1720 cm^{-1} (s). The n.m.r. spectrum contains signals at τ 9.14 (3H, singlet), τ 8.84 (3H, singlet), τ 7.98 (3H, singlet), τ 6.36 (3H, singlet) and τ 5.34 (1H, broad doublet). These data suggest the presence of a carbomethoxy group, an acetoxyl group and two methyl groups attached to saturated carbon atoms. In addition, the presence of an active methylene (1405 cm^{-1}) and a proton (τ 5.34) geminal to an acetoxyl can be inferred. The fact that the n.m.r. spectrum shows only two of the four original C-methyl groups (in amine 29) is indicative of some drastic change during deamination. Chemical degradation of this compound could not

be undertaken because the amounts available were small. However the structure of this compound became apparent when ketoacetate 55a was isolated from the ozonolysis of acetate 402. Direct comparison of ketoacetate 376 and ketoacetate 55a revealed that the two compounds are identical.

Nitroacetate 400

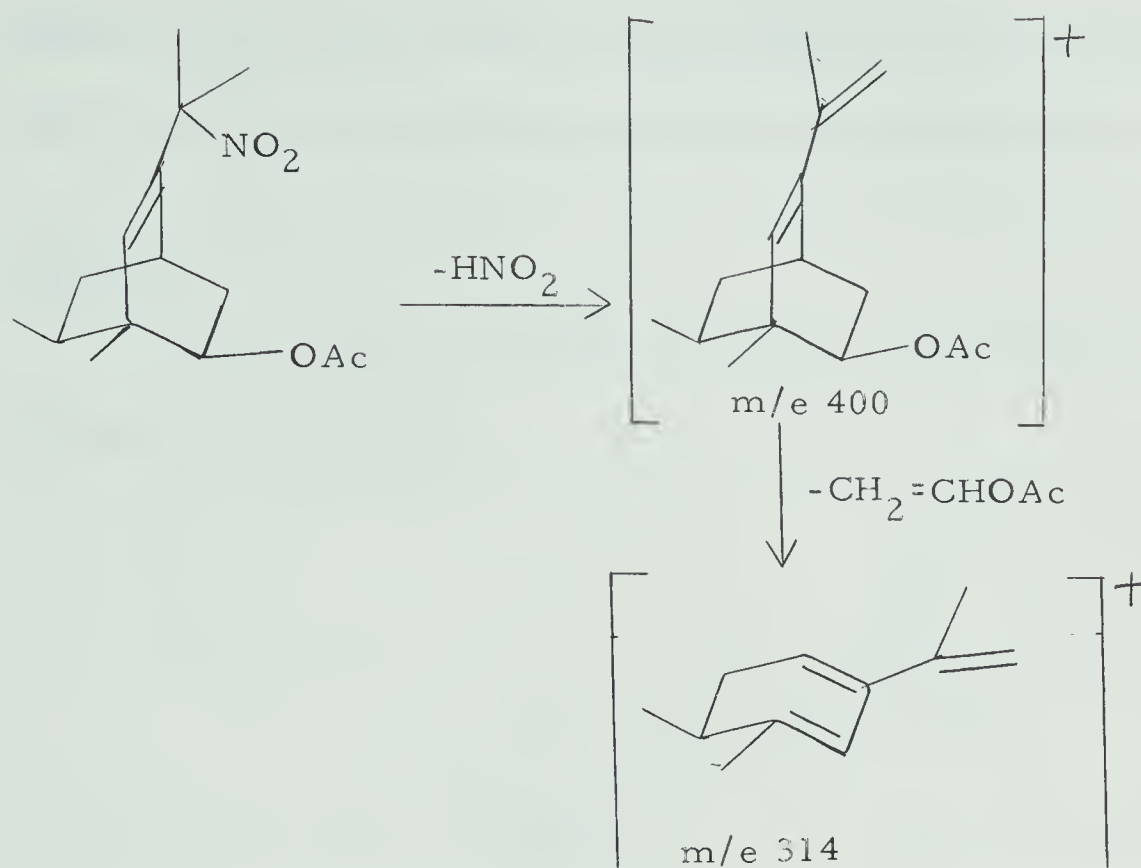
Nitroacetate 400 is assigned structure 57 on the basis of the following considerations.



Elemental analysis of a crystalline sample (m.p. 130-131^o, Skellysolve B) is consistent with the molecular formula C₂₅H₃₇NO₆ (MW 447). The presence of a nitro group was deduced from the infrared spectrum which shows bands at 1340 cm⁻¹ (m) and 1540 cm⁻¹ (s) attributable to the symmetric and asymmetric stretching modes, respectively, of the nitro group. Absorption due to the C-1 carbomethoxy and the C-22 acetoxy groups overlaps to produce a strong band at 1720 cm⁻¹. More information about the structure is revealed by the n.m.r. spectrum of compound 57. The carbomethoxy and the acetoxy groups are characterized by signals at τ 6.35 (3H, singlet)

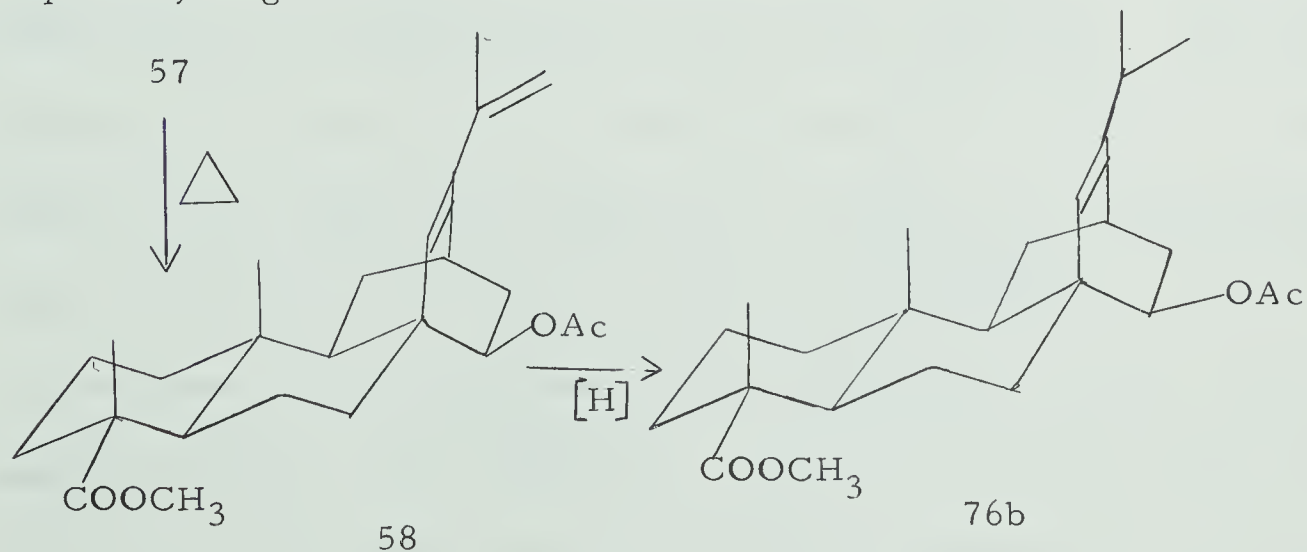
and at τ 8.06 (3H, singlet) respectively. The signal at τ 5.36 (1H, doublet of doublets, $J_{\alpha\beta}$ 8 and 2 c.p.s.) is attributed to the C-22 proton geminal to the acetoxy function. The coupling constants of 8 and 2 c.p.s. for the C-22 proton are consistent with the values observed⁴³ for couplings with vicinal protons in bicyclo[2.2.2]octane system. The presence of such a system is further supported by the highly shielded C-12 methyl group which resonates at τ 9.34, a value in agreement with the values observed in analogous systems considered earlier. The olefinic proton on C-8 appears at τ 4.15 and C-1 methyl group is observed at τ 8.83. The signals (3H each) at τ 8.28 and τ 8.24 are assigned to the methyl groups on C-18. For methyls on a saturated carbon these chemical shifts are low. However, in the light of the known deshielding effect of a nitro group attached to a β -carbon on the protons of an α -carbon these values are not unusual.

The mass spectrum shows the ion of highest mass at m/e 400 which presumably arises by loss of HNO_2 from the parent molecule or the parent ion. Elimination of HNO_2 from tertiary nitro compounds⁴⁸ upon electron impact is well known. The base peak in the mass spectrum of nitroacetate 400 occurs at m/e 314, which can be readily rationalized on the basis of the proposed structure by invoking a retro Diels-Alder reaction as shown.



Confirmation of the structure 57 was sought by attempting the conversion of nitroacetate 400 into acetate 76b by hydrogenolysis of the nitrogen function. The compound resisted hydrogenolysis.

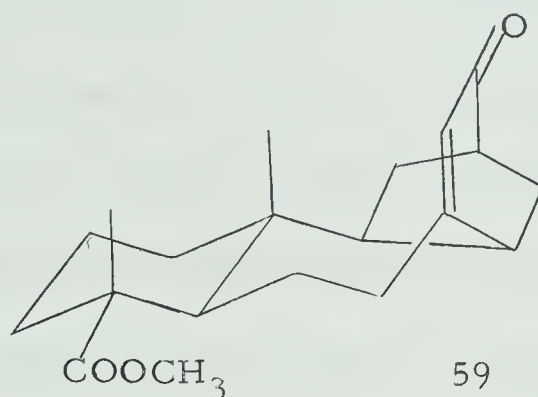
In an alternative approach to the conversion of nitroacetate 400 to acetate 76b the former compound was subjected to pyrolysis expecting that the diene 58 might be produced in the reaction. Subsequent hydrogenation of diene 58 would lead to acetate 76b. This



sequence was unsuccessful since pyrolysis of nitroacetate 400 (280-290^o, 30 mm) resulted in the formation of an intractable product.

Ketone 316

Structure 59 is proposed for ketone 316 on the basis of the following considerations.



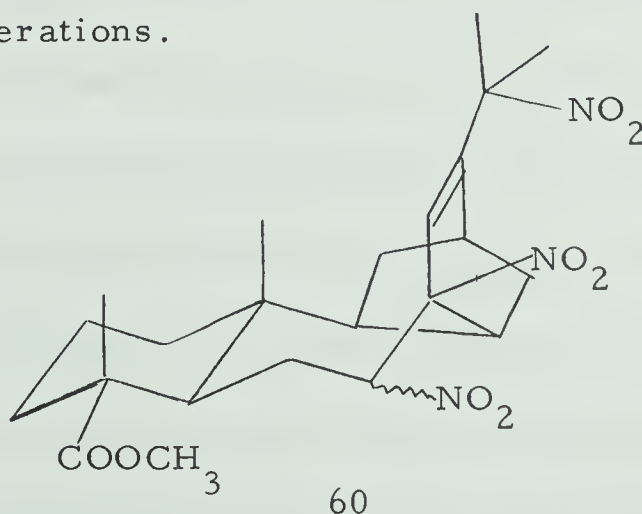
The compound (m.p. 132-133°, crystallized from Skellysolve B) showed a molecular ion at m/e 316. Exact mass measurement revealed the composition of this ion as C₂₀H₂₈O₃ (Calc. 316.2040; Found 316.2044) which is identical with that of the ketoolefin 56. The fragmentation patterns shown by the two compounds in the mass spectra are however very different. In common with ketoolefin 56, ketone 316 shows only two C-methyl groups in the n.m.r. spectrum. The methyl group on C-12 appears at τ 9.18 and the one on C-1 at τ 8.77. The absence of any signals attributable to an isopropyl or an isopropylidene group indicated that this moiety is lost during deamination. The carbo-methoxy group is characterized in the infrared spectrum by a strong band at 1720 cm⁻¹ and in the n.m.r. spectrum by a three proton singlet at τ 6.33. The olefinic proton on the trisubstituted double bond gives

rise to a signal at τ 4.38 (1H, singlet) in the n.m.r. spectrum. The presence of a conjugated ketonic function is indicated by bands at 1625 cm^{-1} (m, C=C) and 1670 cm^{-1} (s, >C=O) in the infrared spectrum and confirmed by the absorption at $243\text{ m}\mu$ ($\epsilon = 11,080$) in the u.v. spectrum of ketone 316.

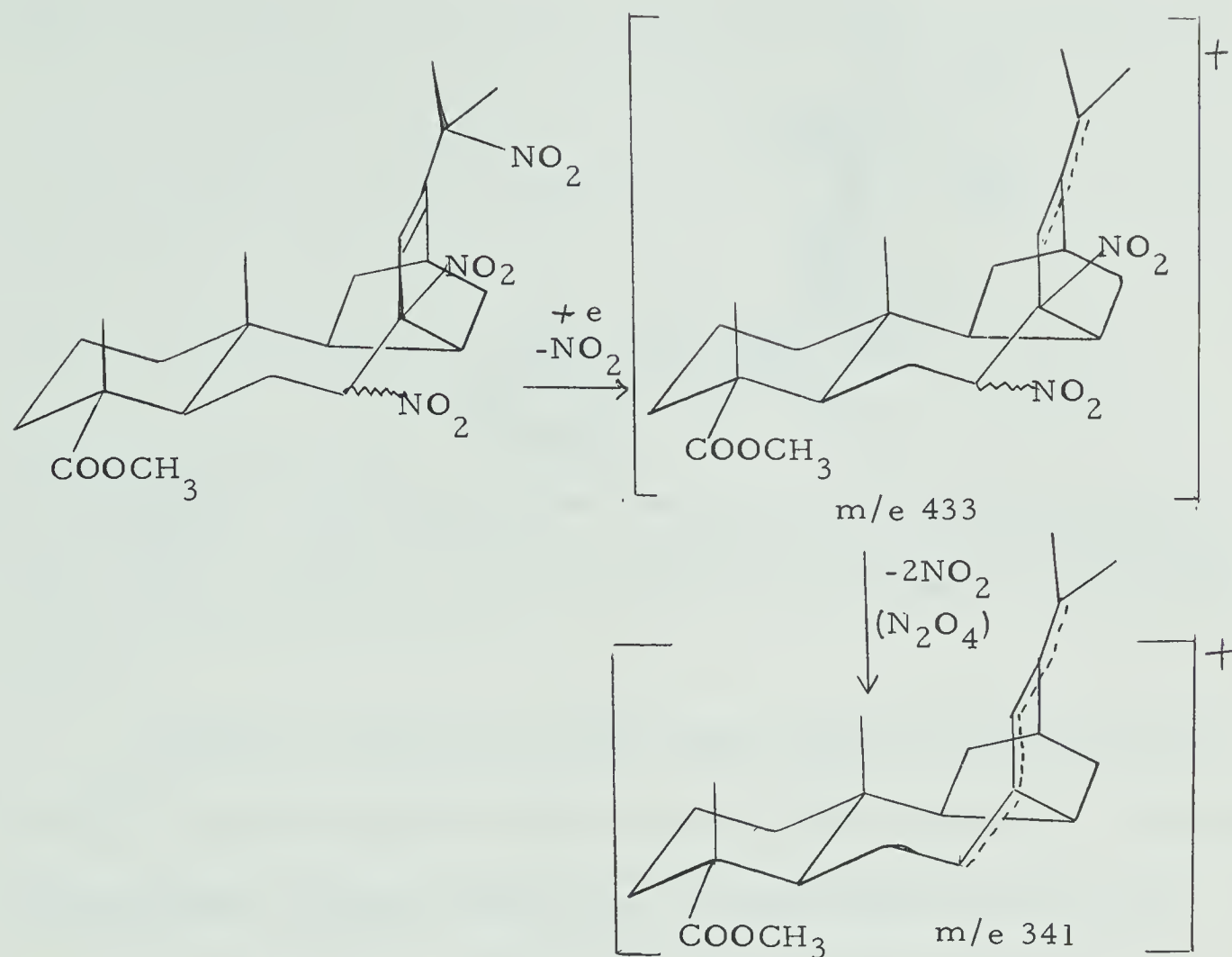
It is reasonable to assume that, by analogy with ketoacetate 376, the ketonic function of ketone 316 is produced by loss of the isopropyl group during deamination. Since an α,β unsaturated ketone cannot be formed in the original bicyclo[2.2.2]octane system without violating Bredt's rule it follows that ketone 316 does not possess this system. All the spectral data for ketone 316 can be rationalized on the basis of a bicyclo[3.2.1]octane system as shown in structure 59. Preparation of ketone 316 by controlled ozonolysis of diene 82a confirms the proposed structure (see Chapter III).

The Trinitro Compound

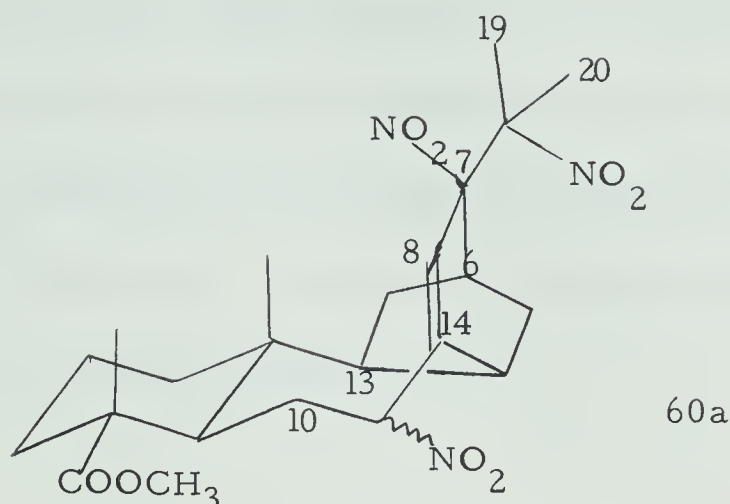
Structure 60 is proposed for the trinitro compound on the basis of the following considerations.



The molecular formula of the trinitro compound was deduced from a consideration of its mass spectrum and the results of its elemental analysis. The highest peak in the mass spectrum appeared at m/e 433 which can be explained on the basis of loss of an NO_2 radical from the molecular ion (m/e 479, not observed in the spectrum). The elemental analysis of a pure sample (m.p. $177-178^\circ$, crystallized from ethanol) is consistent with the molecular formula $\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_8$ (MW 479). The molecular weight (509) determined by osmometric method is also in reasonable agreement. The presence of the nitro groups is suggested by the infrared spectrum which shows bands at 1325 cm^{-1} (m), 1350 cm^{-1} (m), 1550 cm^{-1} (s), and 1570 cm^{-1} (s). Absorption characteristic of nitrite or nitrate functions is absent. Since two of the eight oxygen atoms of compound 60 are associated with the C-1 carbomethoxy group (IR 1725 cm^{-1} , NMR δ 6.25) it is reasonable to assume the presence of three nitro groups to account for the three nitrogen atoms and the remaining six oxygen atoms. This assumption gains support from the appearance of the base peak at m/e 341 in the mass spectrum which can be rationalized on the basis of structure 60 in terms of the following fragmentation pattern (one possible way). The composition of the ion at m/e 341 as $\text{C}_{23}\text{H}_{33}\text{O}_2$ was confirmed by exact mass measurement (Calc: 341.2481, Found: 341.2485). Taking into consideration the presence of three nitro groups and one carbomethoxy group a reasonable postulation can be made that the trinitro



compound has four rings and one carbon-carbon double bond. In agreement with this the n.m.r. spectrum shows a signal at τ 3.90 (1H, br. s.) attributable to the olefinic proton on C-8. The low field signal at τ 5.12 (1H, m) is attributed to the proton on C-9 which bears an electron withdrawing nitro group. Spin decoupling experiments showed there was no coupling between the C-8 and the C-9 protons, which favors the presence of the vicinal C-9 and C-14 nitro groups rather than the vinylogous C-9 and C-7 nitro groups (most of the evidence can be rationalized in terms of the latter alternative indicated by structure 60a). Two of the four C-methyl signals in the n.m.r. spectrum of compound 60 appear at τ 8.93 (C-12 methyl) and τ 8.63



(C-1 methyl). The remaining two methyl groups (C-18) resonate at τ 8.21 (6H, s), which is consistent with the presence of a nitro group on C-18.

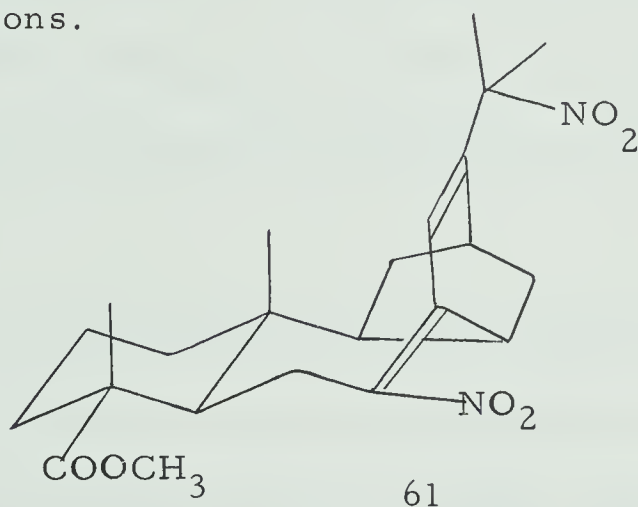
In order to obtain more information about the environment of the \triangle^{7-8} double bond the trinitro compound was subjected to reactions with perbenzoic acid and with ozone. In both cases only starting material was obtained. The failure of the trinitro compound to undergo these reactions is not unexpected since a carbon-carbon double bond in the vicinity of a nitro group is known⁴⁹ to be inert in many such reactions.

Compound 60 was next subjected to a reaction which involved elimination of nitrous acid on basic alumina. Compounds with vicinal nitro groups are known⁵⁰ to eliminate nitrous acid to give nitroalkenes under the influence of a base. It was felt that the desired elimination of HNO₂ in compound 60 might be effected on basic alumina. Accordingly a chloroform solution of the trinitro compound was filtered through a short column of alumina, and furnished a crystalline substance in

quantitative yield. Comparison of the properties of this substance with those of the dinitro compound mentioned earlier revealed that the two are identical. This establishes a correlation between the trinitro compound and the dinitro compound. Evidence in support of the structure of the latter compound will be presented now.

The Dinitro Compound

Structure 61 is assigned to the dinitro compound on the basis of the following considerations.

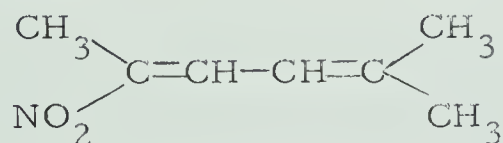


The mass spectrum of compound 61 gave a molecular ion at m/e 432 (very weak) which is consistent with the molecular formula $C_{23}H_{32}N_2O_6$. Elemental analysis of a pure sample (m.p. 136-137°, crystallized from ethanol) also supported this formulation. As would be expected for the proposed structure 61, the infrared spectrum indicates the presence of two nitro groups, one of which is vinylic (1320 cm^{-1} , 1500 cm^{-1}) and the other of which is attached to saturated carbon (1545 cm^{-1} , 1350 cm^{-1}). The n.m.r. spectrum is consistent with the proposed structure. Thus the C-18 methyls resonate at τ 8.24 and τ 8.20, analogous to the values observed for these methyls

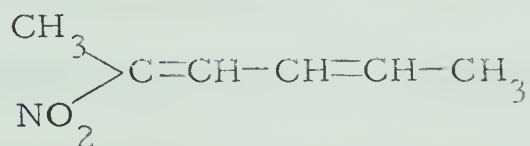
in the nitroacetate 400. The C-1 methyl and C-1 carbomethoxyl signals appear at τ 8.54 and τ 6.32 respectively. The signal at τ 9.32 is attributed to the C-12 methyl group which now lies in the shielding cone of the \triangle^{9-14} double bond as indicated by examination of a molecular model. The olefinic proton on C-8 gives rise to a signal (singlet) at τ 2.80, which is a considerably lower chemical shift than that usually observed for an olefinic proton. The cause for the lower chemical shift of the C-8 proton appears to be the deshielding effect of the C-9 nitro group. Whether this deshielding is the result of an inductive or an anisotropic effect (or both) of the nitro group is uncertain.

Further evidence concerning the structure of the dinitro compound is revealed by the u.v. spectrum, which shows absorption at 229 m μ (ϵ_{max} , 6750) and 348 m μ (ϵ_{max} , 6190). These values are consistent with those reported⁵¹ for analogous chromophoric systems*.

*



EtOH
max 230 m μ (ϵ_{max} , 7700);
335 m μ (ϵ_{max} , 11700)

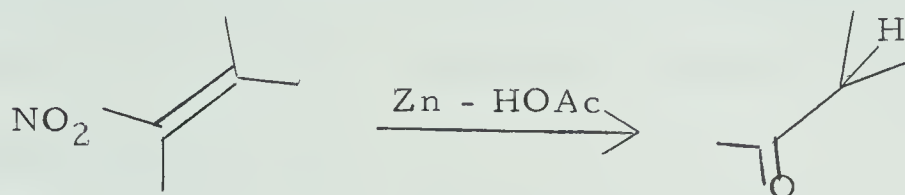


EtOH
max 212 m μ (ϵ_{max} , 10100);
235 m μ (ϵ_{max} , 5100);
309 m μ (ϵ_{max} , 10000)

Expected value for 61 335+20 m μ = 355 m μ

Attempted pyrolytic elimination of nitrous acid from 61 led to a very complex mixture of products.

The transformation of the dinitro compound to a β, γ unsaturated ketone was attempted. The conversion of a conjugated nitroalkene to a ketone by reduction with Zn-HOAc is a known reaction.



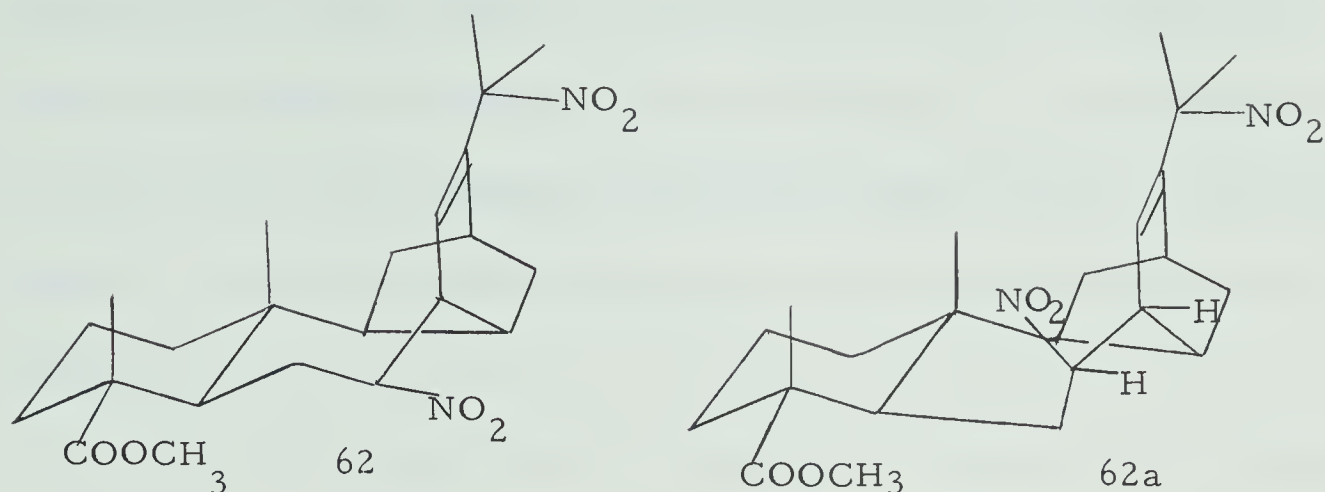
Following the procedure of Dodson and Rigel⁵² an aqueous acetic acid solution of compound 61 was treated with zinc dust. The original yellow color of the solution rapidly disappeared indicating that the chromophoric system had been destroyed. The infrared spectrum of the reduction product showed weak absorption (1700 cm^{-1} , shoulder) suggestive of a ketone which, however, could not be isolated due to the complex nature of the product. Attention was then turned to catalytic hydrogenation.

The dinitro compound was hydrogenated over Adam's catalyst in ethanol. The product obtained from this reaction showed a band at 3580 cm^{-1} (m) in the infrared spectrum suggesting that a hydroxylic compound had been formed during the hydrogenation. Acetylation of the hydrogenation product afforded material which showed absorption attributable to an O-acetyl group (1760 cm^{-1}) and a secondary amide (1545 cm^{-1} , 1670 cm^{-1} , 3400 cm^{-1} (w)). The acetylated material was subjected to chromatography over alumina and a crystalline compound

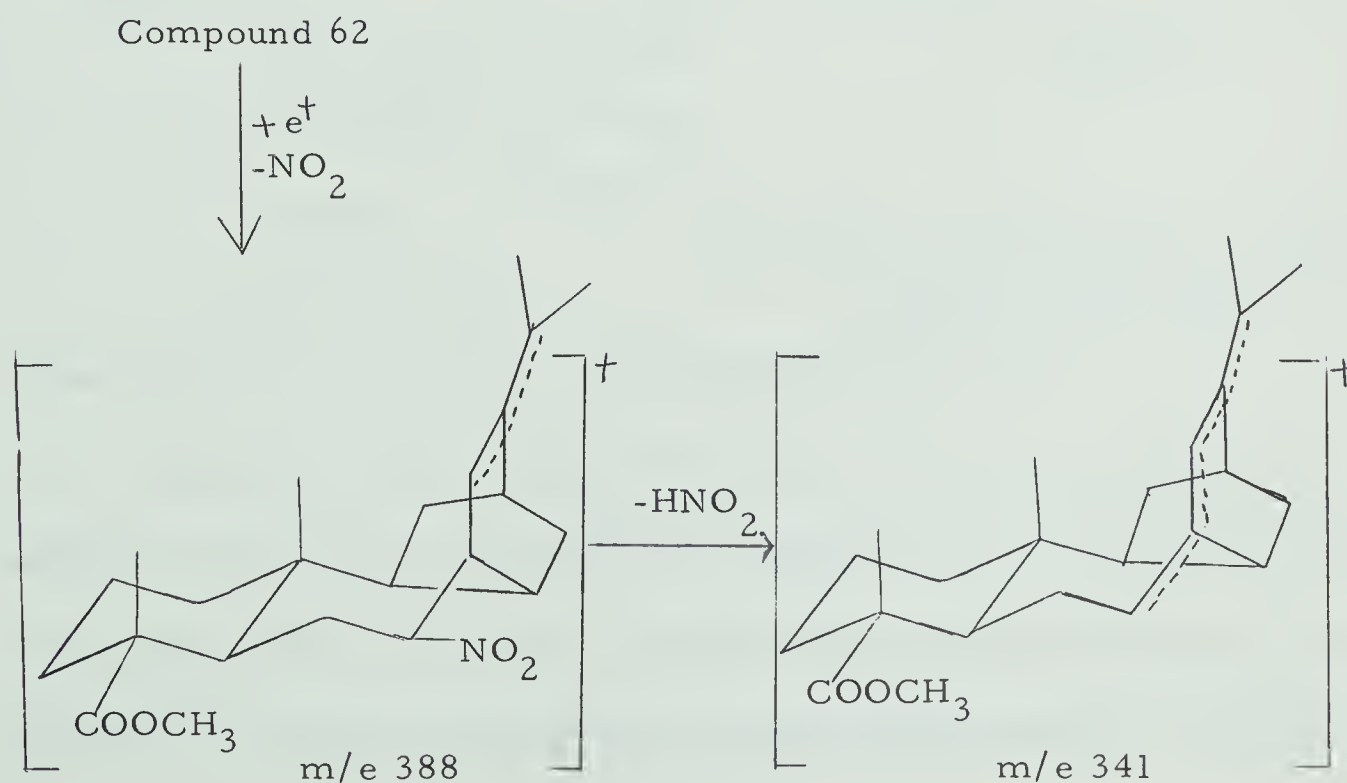
(ca. 15% overall yield), henceforth referred to as the N-acetate I, was obtained from the fractions eluted with benzene. Later fractions eluted with more polar solvents afforded a small amount of material which also appeared (infrared spectrum) to be an amide. None of the O-acetyl compound could be obtained from the chromatography. Structure 63 is assigned to N-Acetate I. Evidence in support of this structure will be presented later (p. 93).

In order to determine whether the formation of the hydroxylic compound produced during the catalytic hydrogenation in 95% ethanol required the presence of water at some stage the reduction of the dinitro compound was carried out in ethyl acetate. The reduction product again showed the presence of a hydroxylic substance as judged from the infrared spectrum (band at 3580 cm^{-1}). Acetylation ($\text{Ac}_2\text{O/py}$) of the reduction product afforded a mixture which showed absorption attributable to O-acetyl and N-acetyl functions. In hopes of isolating the O-acetyl compound(s) the acetylated material was subjected to chromatography on silica gel. Although the chromatography was not effective in the separation of the O-acetate(s) it afforded a crystalline product (ca. 8% overall yield) for which structure 62 is proposed. Further chromatography of the residual O-acetate-N-acetate mixture on alumina gave a small amount of N-acetate I.

Compound 62 (m.p. $140-140.5^\circ$, crystallized from ethanol) gave an analysis consistent with the molecular formula $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$ (MW 434).

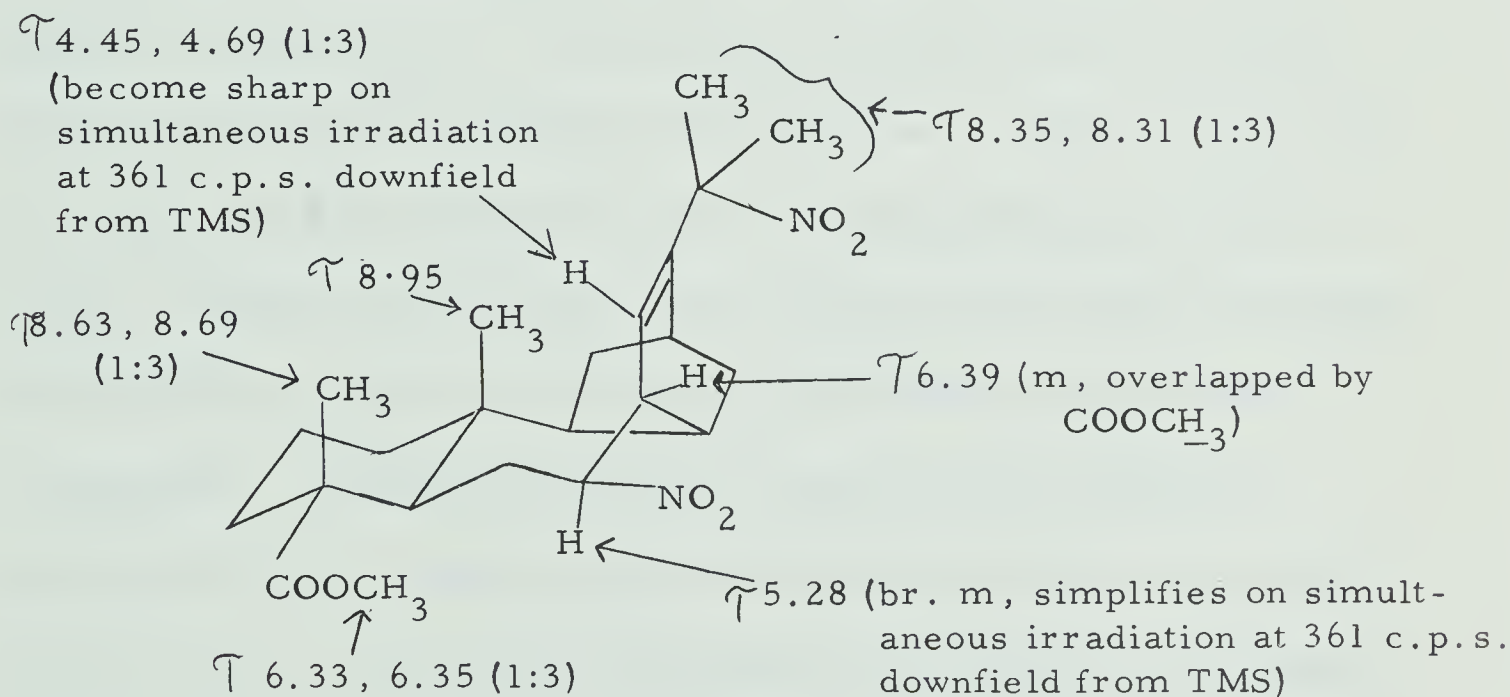


The mass spectrum showed the ion of the highest mass at m/e 388 which presumably arises from the molecular ion (not observed in the spectrum) by loss of NO_2 , analogous to the case of trinitro compound. The base peak occurs at m/e 341 which is indicative of a loss of 47 (HNO_2) from the peak at m/e 388. Appearance of this peak can be rationalized as depicted below. The composition of the ions m/e 388 and 341 as $\text{C}_{23}\text{H}_{34}\text{NO}_4$ and $\text{C}_{23}\text{H}_{33}\text{O}_2$ respectively was confirmed by exact mass measurement.



The presence of nitro groups is indicated by the infrared spectrum which shows bands at 1350 cm^{-1} (m) and 1540 cm^{-1} (s) attributable to the symmetric and asymmetric stretching modes of NO_2 on saturated carbon. The C-1 carbomethoxyl gives rise to strong absorption at 1720 cm^{-1} .

The n.m.r. spectrum of compound 62 shows an unusual feature in that many of the protons exhibit nonequivalence. We believe that this nonequivalence may be explained by the importance of two different conformers (ratio 1:3) in describing the structure of 62. The accompanying diagram indicates the chemical shifts of the protons concerned.



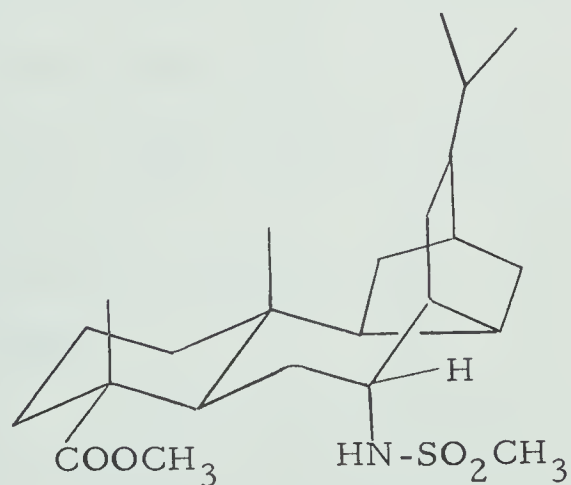
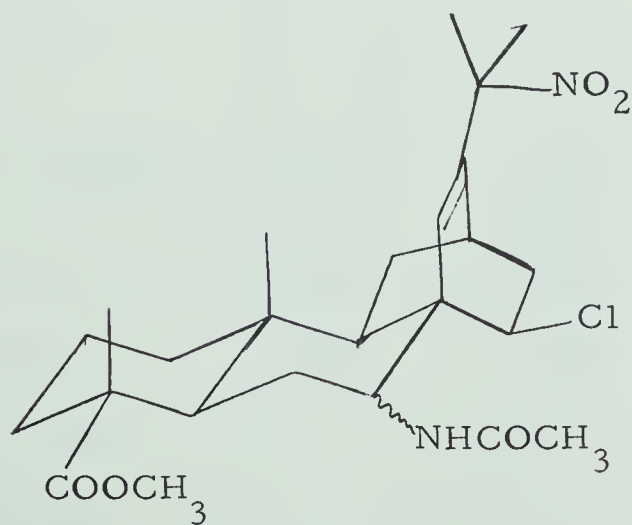
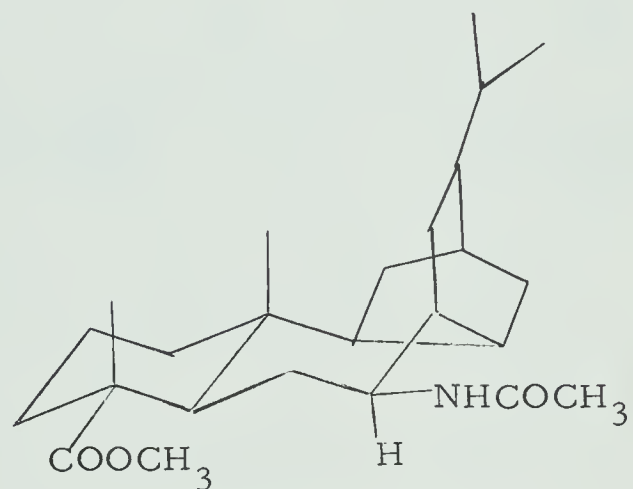
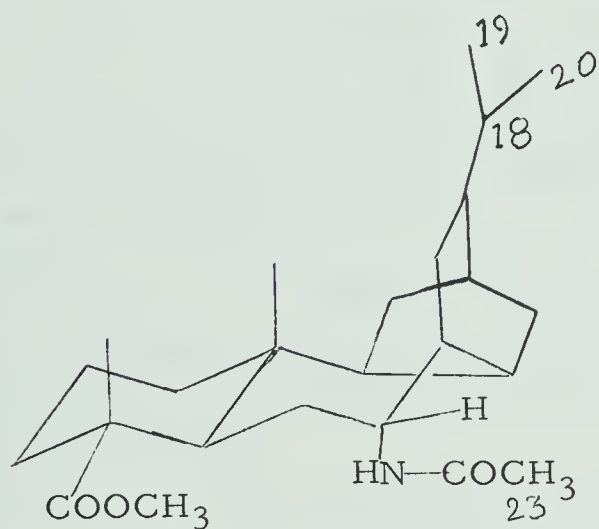
These values are consistent with the formulation in 62.

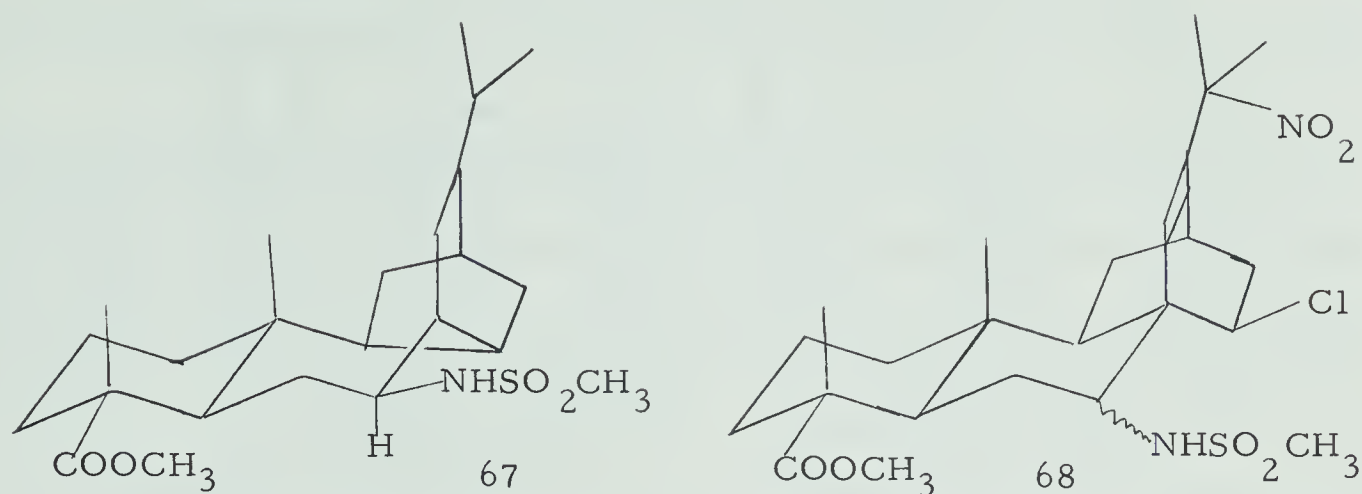
It is possible to rationalize the observed nonequivalence of the protons in the n.m.r. spectrum of 62 on the basis of a presence of two compounds epimeric at C-9. Compound 62, however, showed a single spot on t.l.c. and a recrystallized sample (sharp melting, $140-140.5^\circ$)

showed an n.m.r. spectrum identical with that obtained before recrystallization. This militates against the presence of two epimeric compounds. Consequently, we feel the observed nonequivalence is best explained on the basis of the presence of two conformers indicated by 62 (7 membered ring in chair form) and 62a (7 membered ring in boat form).

As pointed out earlier catalytic hydrogenation of the dinitro compound, carried out in ethanol or ethyl acetate, gives hydroxylic compounds. The hydroxyl group probably occurs in the form of an hydroxylamine produced by partial reduction of one or both nitro groups in compound 61. Nitro groups are known to form hydroxylamine derivatives⁵³ on catalytic hydrogenation. Unless the hydroxyl group is activated, further reduction of hydroxylamines to amines is slow. It was felt that use of an acid catalyst in the catalytic hydrogenation might be effective in minimizing the formation of hydroxylic compounds. Accordingly the dinitro compound was subjected to hydrogenation over Adams' catalyst in ethanol containing a few drops of conc. HCl. The product thus obtained was separated into nonbasic and basic fractions. This resulted in the isolation of a basic product in ca. 85% yield. Acetylation of the basic fraction afforded material which on crystallization from methanol gave the crystalline N-acetate I in ca. 55% yield. The noncrystalline residue was subjected to chromatography (Al_2O_3) and gave, in addition to further N-acetate I, two other

compounds, referred to as N-acetate II and chloro N-acetate, in overall yields of ca. 10% of each. In a parallel experiment the basic product obtained by catalytic reduction of the dinitro compound was treated with methanesulfonyl chloride in pyridine to give a mixture of sulfonamides. Separation of these furnished sulfonamide I (ca. 55%), sulfonamide II (ca. 5%), and chlorosulfonamide (ca. 15%). Structures 63-68 are proposed for N-acetate I, N-acetate II, chloro N-acetate, sulfonamide I, sulfonamide II, and chlorosulfonamide, respectively.





Tables I-III summarize the relevant spectral data of compounds 63-68.

TABLE I- Mass Spectra of Compounds 63-68

	63	64	65	66	67	68
Parent Peak or peak of highest mass	403 (M)	403 (M)	482 (M) 480 (M)	439 (M)	439 (M)	472 (M-46) 470 (M-46)
Base Peak	344	344	398	344	344	144
Other relevant peaks			38, 36			38, 36

TABLE II - I.R. Spectra of Compounds 63-68

	63	64	65	66	67	68
N-H	3370 (br)	3440	3435	3225	3380	3360
C ₁ -COOCH ₃	1715	1725	1725	1705	1720	1720
amide I	1660	1675	1675	-	-	-
amide II	1540	1540	1500	-	-	-
ν_{as} SO ₂	-	-	-	1330	1340	1340
ν_s SO ₂	-	-	-	1150	1150	1140
NO ₂			1540			1545

TABLE III - N.M.R. Spectra of Compounds 63-68

	63	64	65	66	67	68
C_1-CH_3	8.75	8.72	8.83	8.75	8.78	8.82
$C_{12}-CH_3$	8.87	8.88	9.27	8.88	8.89	9.30
$ \begin{array}{c} \text{CH}_3 \\ \diagup \\ C_{18} \\ \diagdown \\ \text{CH}_3 \end{array} $	9.15 (d) 9.14 (d) J=6 cps	9.13 (d) 9.11 (d) J=6 cps	8.25 8.21	9.16 (d) 9.13 (d) J=6 cps	9.11 (d) 9.10 (d) J=6 cps	8.26 8.22
$-C_{23}H_3$	8.00	8.06	7.91	7.12	7.09	6.90
$C_1-COOCH_3$	6.33	6.26	6.35	6.32	6.34	6.29
C_9-H	6.34 (br. s)	<u>6.10</u>	<u>5.95</u> (br. d)	6.70 (br.)	6.54 (br.)	5.97 (br. d) J=10 cps
N-H	3.0 (br. s)	<u>4.66</u>	<u>3.97</u>	3.87 (br. d) J=6 cps	5.66 (d) J=7.5 cps	5.07 (d) J=10 cps
C_8-H	-	-	4.22	-	-	4.19
$C_{22}-H$			<u>5.37</u> (br. d)			5.72 (d. of d) J=8.5 & 3 cps

The underlined signals not well defined due to the poor quality of the spectra (determined on small quantities).

N-acetate I (63) and N-acetate II (64).

N-acetate I (m.p. $80-81^\circ$, crystallized from methanol showed a parent peak at m/e 403 in the mass spectrum. Exact mass determination revealed the composition of this peak as $C_{25}H_{41}NO_3$ (Found, 403.3081, Calc. 403.3086). The elemental analysis of a pure sample

of N-acetate I was consistent with this molecular formula.

N-acetate II could not be obtained in completely pure form. Apparently a nitro compound was present as an impurity as judged by the infrared spectrum. The mass spectrum of N-acetate II was, however, satisfactory and was almost identical with that of N-acetate I.

Tables II and III give details of the infrared and n.m.r. spectra of the two compounds. Some features of the spectral data are significant and deserve comment. The signal attributed to the C-9 H in the n.m.r. spectrum (CDCl_3) of 63 is overlapped by the signal due to the C-1 carbomethoxyl. When the spectrum was determined in deuterated pyridine the two signals separated. The methyl group of the C-1 carbomethoxyl now appeared at τ 6.36 and the C-9 proton resonated at τ 6.08 (br. s). The change of solvent also affected the chemical shift of the proton on the nitrogen atom which appeared at τ 2.57 (br. s) in pyridine. Simultaneous irradiation 743 c.p.s. downfield from TMS (NH signal) caused a decrease in the width at half height of the signal at τ 6.08 from ≈ 15 c.p.s. to ≈ 10 c.p.s.. This fact confirmed the assignment made for the protons on C-9 and on nitrogen.

Comparison of the infrared spectra of compounds 63 and 64 reveals that the bands attributed to the C-1 COOMe and N-H occur at lower frequency in the former compound. Furthermore the absorption due to the N-H (3370 cm^{-1}) in 63 is relatively broad. Comparison of the n.m.r. spectra of the two compounds indicates that the chemical

shift of the N-H in 63 is lower by ca. 1.6 p.p.m.. A possible reason for the differences in the infrared and the n.m.r. spectra of N-acetate I and N-acetate II is that the C-1 COOMe and C-9 NHCOCH_3 are intramolecularly hydrogen bonded in the former compound. Examination of a molecular model of 63 indicates that the carbonyl of the C-1 COOMe and the C-9 N-H are close enough to be intramolecularly H-bonded provided that the latter group is χ -oriented (i.e., axial in a twist chair form of the 7-membered ring). Support for the χ -orientation of the amido group on C-9 (in compound 63) comes from the fact that the n.m.r. spectrum of this compound shows a relatively narrow signal ($W \frac{h}{2} \approx 10$ c.p.s. on decoupling the N-H) for the C-9 H, which is suggestive of its equatorial nature. An axial proton with three vicinal hydrogens would be expected to give a much broader signal. For these reasons the amide function in N-acetate I is assigned the χ -configuration. Detailed investigation of the isomeric compound 64 could not be undertaken since it was available in very small quantity. The available evidence (especially the similarity of its mass spectrum to that of 63) indicates that it is epimeric with compound 63 at C-9.

Sulfonamide I and Sulfonamide II

Sulfonamide I (66) and Sulfonamide II (67) are isomeric compounds analogous to N-acetate I and N-acetate II. The molecular formulas of compounds 66 and 67 were determined by measuring the exact mass of the molecular ion (Found 439.2752 for each, Calc. 439.2757 for

$C_{24}H_{41}NO_4^{32}S$). The infrared and n.m.r. spectra of these compounds are consistent with the proposed structures. A comparison of the spectral properties of sulfonamide I with those of sulfonamide II is revealing. The C-1 COOMe and C-9 N-H in the former compound show absorption at lower frequency in the infrared spectrum. The absorption due to N-H in compound 66 is relatively broad. The n.m.r. spectrum of compound 66 shows the N-H at lower field (Δ 1.8 p.p.m.). The behaviour of the sulfonamide is thus closely analogous to that of N-acetate I. Using the same arguments as in the case of the N-acetyl compounds structure 66 is proposed for sulfonamide I. Structure 67 then follows for the epimeric sulfonamide II.

It is interesting to note that the n.m.r. spectra of the four compounds considered so far show pairs of doublets for the C-18 methyl groups. The nonequivalence of these methyl groups is consistent with the asymmetric environment⁵⁴ at C-8.

Chloro N-acetate 65 and Chlorosulfonamide 68

The remaining two compounds in this series, 65 and 68, differ from the compounds considered above in that, unlike the latter, they 1) retain a nitro group, 2) contain a chlorine atom, and 3) possess a bicyclo[2.2.2]octane system in the C/D ring portion.

The molecular formula of compound 65 was determined mass spectrometrically from the measurement of the exact mass of the parent peak at m/e 480 (Found 480.2395, Calc. 480.2392 for $C_{25}H_{37}N_2O_5^{35}Cl$).

As would be expected⁵⁵ from the natural abundance of ³⁷Cl, the mass spectrum shows a peak at m/e 482 which is approximately one third as intense as the peak at m/e 480. Further support for the presence of a chlorine atom comes from the occurrence of peaks at m/e 36 and 38 ($\approx 3:1$) attributable to the ions $[\text{H}^{35}\text{Cl}]^+$ and $[\text{H}^{37}\text{Cl}]^+$ respectively. The presence of a nitro group in compound 65 was deduced from the infrared spectrum which shows bands at 1350 cm^{-1} and 1540 cm^{-1} . The n.m.r. spectrum of compound 65 is rather poorly resolved since the amount of sample available for determination of the spectrum was small. Structure 65 is proposed for this compound by analogy to chlorosulfonamide 68 which was examined in a more detailed way.

Compound 68 did not show a parent peak in the mass spectrum. The molecular formula $\text{C}_{24}\text{H}_{37}\text{N}_2\text{O}_6$ ^{32 35} S^{35}Cl (MW 516) was inferred from the composition of the ion of highest mass at m/e 470 (Found 470.2129, Calc. 470.2129 for $\text{C}_{24}\text{H}_{37}\text{NO}_4$ ^{32 35} S^{35}Cl) which presumably arises from the molecular ion by loss of NO_2 . The presence of the nitro group is indicated by the infrared spectrum which shows bands at 1345 cm^{-1} (m) and 1545 cm^{-1} (s). The n.m.r. spectrum of 68 was very informative.

The C-18 methyl groups appear at τ 8.26 and τ 8.22, similar in chemical shift to those of the parent dinitro compound 61. The signal at τ 9.30 is attributed to the C-12 methyl group which lies in the shielding region of the \triangle^{7-8} double bond. The chemical shift of the

C-12 methyl is reminiscent of similar compounds possessing the bicyclo- $[2.2.2]$ octane system. The signal at τ 5.72 (doublet of doublets, $J \approx 8.5$ and 3 c.p.s.) is assigned to the proton on C-22. The splitting pattern shown by the signal at τ 5.72 is analogous⁴³ to the patterns observed in bicyclo $[2.2.2]$ octane systems. In order to test this assignment spin decoupling experiments were undertaken. The accompanying diagram and Table IV indicate the results of these experiments.

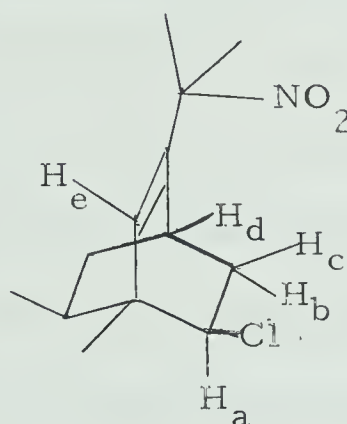


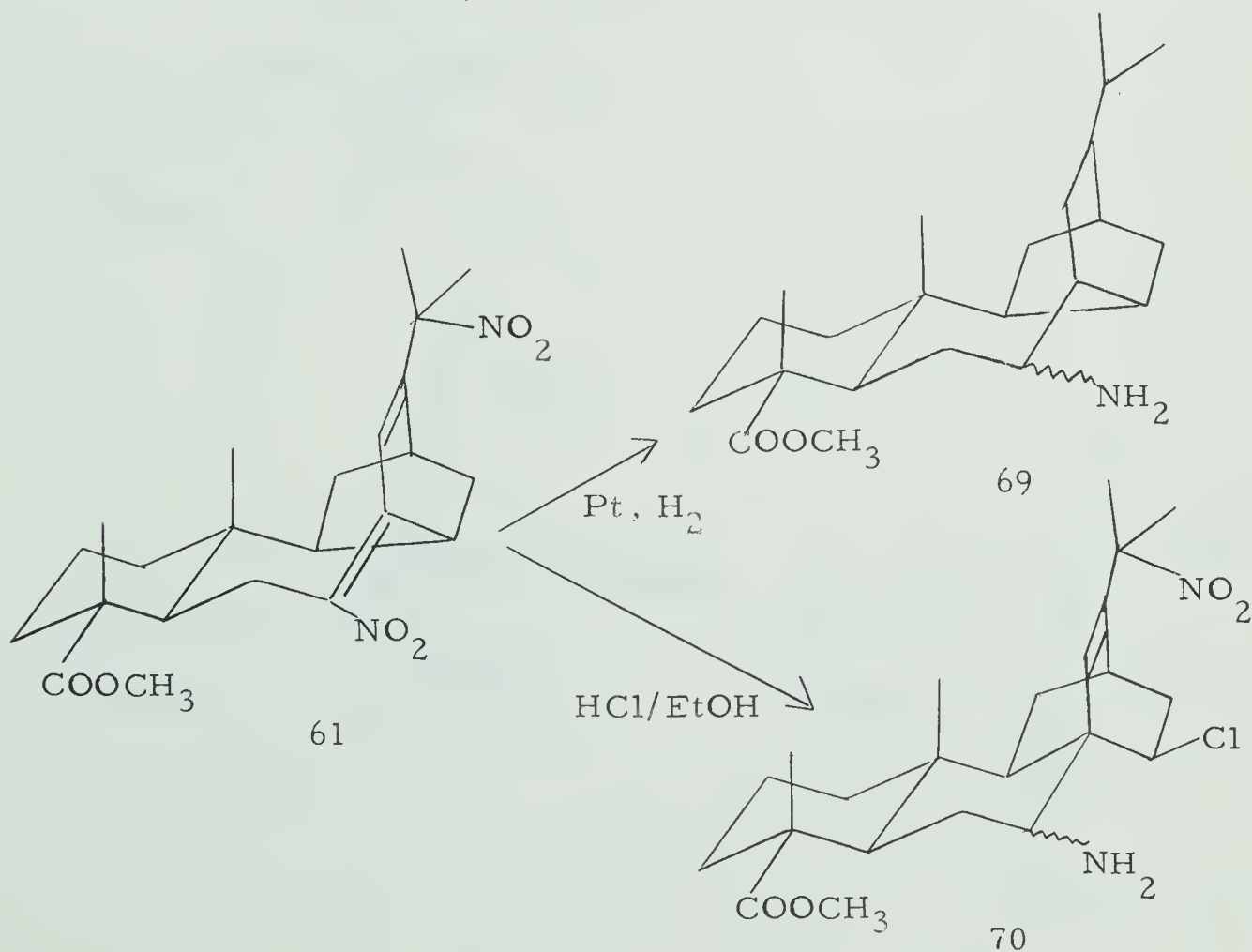
TABLE IV

Proton	Chemical Shift in c.p.s. downfield from TMS (τ , multiplicity)	Simultaneous irradiation at -----
H _e	585 (4.15, br. s)	
H _d	240 (7.60, m)	585 c.p.s. causes sharpening 229 c.p.s. causes simplification
H _c & H _b	229 (7.71, m)	
H _a	428 (5.72, d. of d.)	229 c.p.s. causes collapse to a br. s.

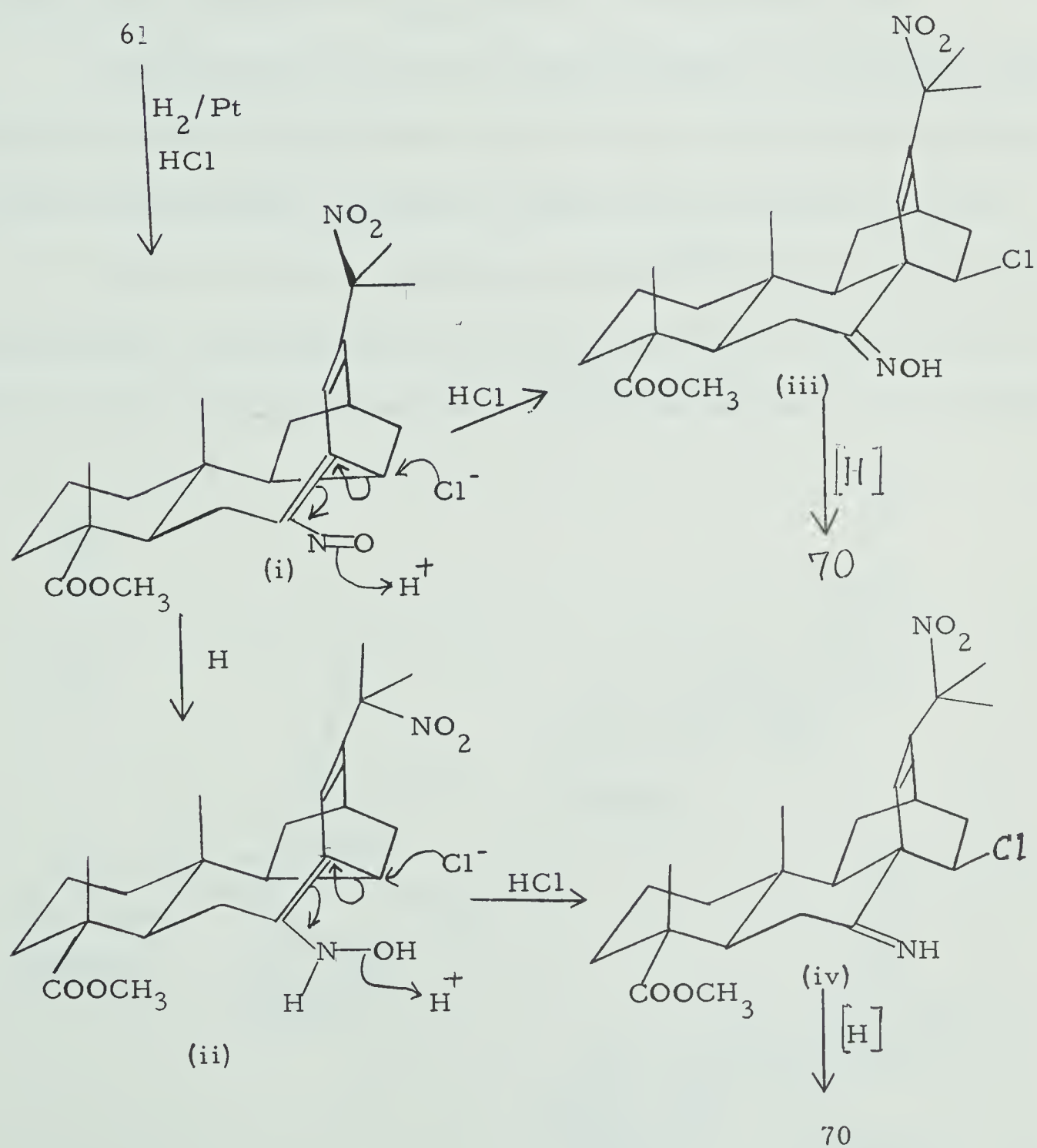
The results of the spin-decoupling experiments are thus in agreement with the proposed structure.

The n.m.r. spectrum of compound 68 shows two more protons in the low field region. The signal at τ 5.97 (br. d. $J \approx 10$ c.p.s.) is attributed to the proton on C-9 and the one at τ 5.07 (br. d. $J \approx 10$ c.p.s.) is assigned to the proton on the nitrogen in the sulfonamido group. Coupling ($J \approx 10$ c.p.s.) between these two protons was shown by decoupling experiments. The width at half height of the signal at τ 5.97 (≈ 7 c.p.s. on simultaneous irradiation 493 c.p.s. downfield from TMS) indicates that the C-9 proton is probably equatorial.

Compounds 63, 64, 66, 67 are derived from the precursor amine 69 produced by catalytic hydrogenation of the dinitro compound. Compounds 65 and 68 are derived from the amine 70, the formation of which involves acid-catalyzed rearrangement and catalytic reduction.



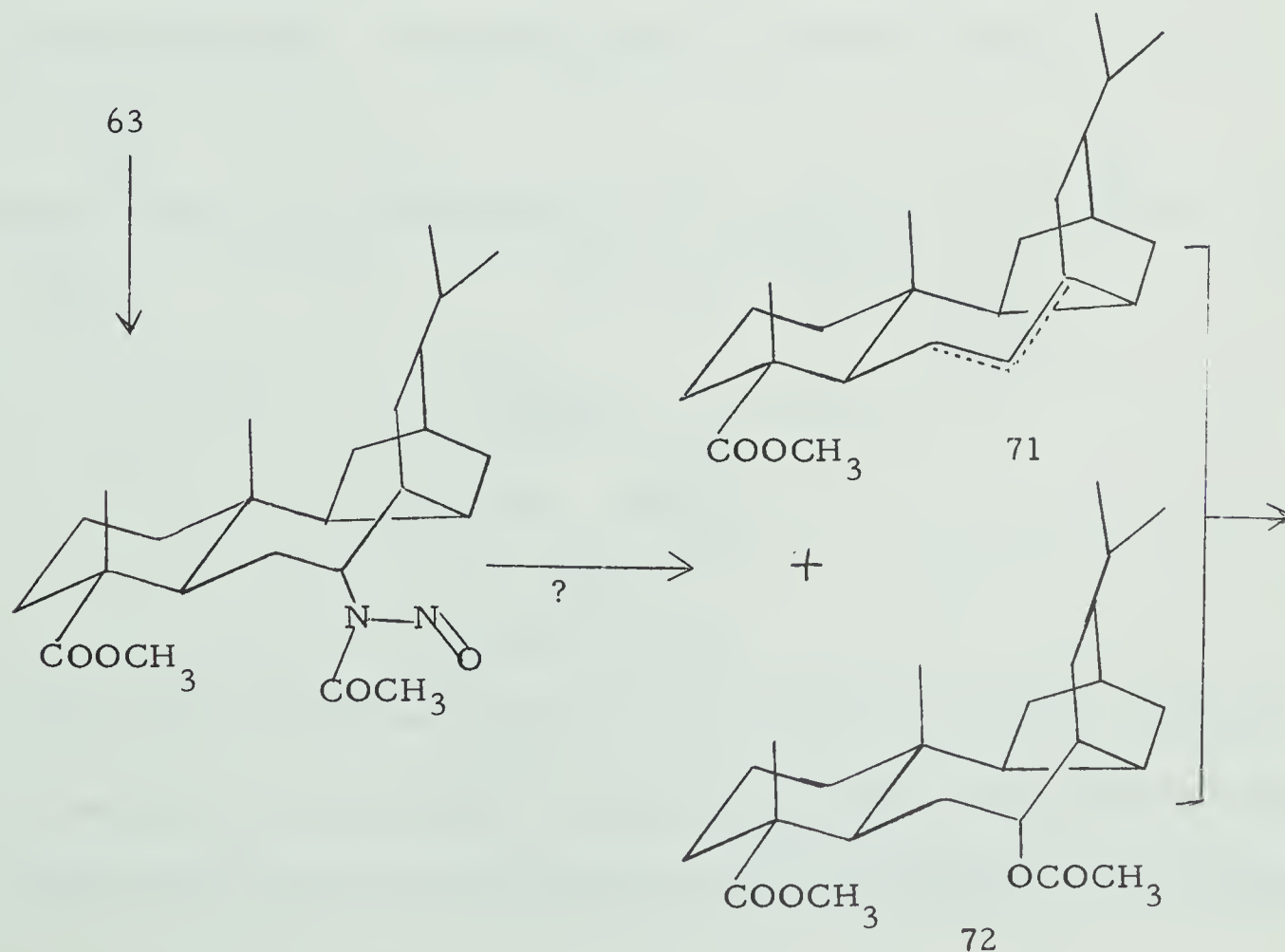
The genesis of amine 69 is straightforward. Apparently catalytic hydrogenation of the dinitro compound 61 is initiated at the C-9 and C-18 nitro groups. Hydrogenolysis of the C-18 nitrogen function followed by reduction of the remaining unsaturated centres gives amine 69. Two ways in which amine 70 might be formed are indicated below.

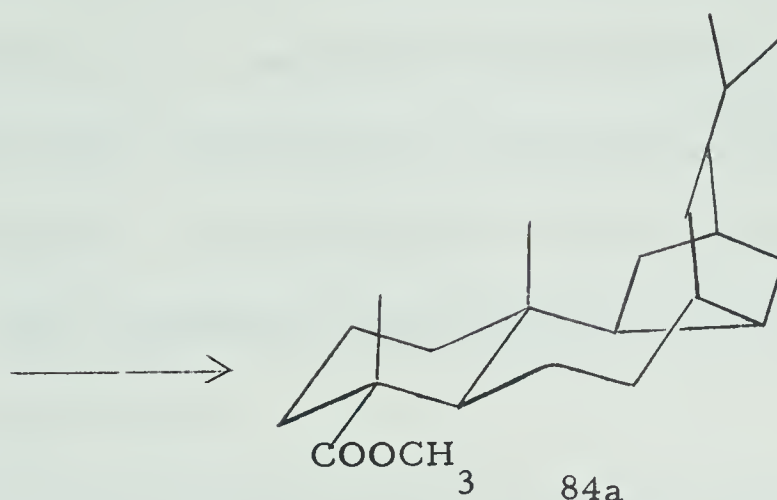


These involve initial reduction of the C-9 nitro group to a nitroso or a hydroxylamino group as shown in structures (i) and (ii) respectively. The intermediates (i) and (ii) could undergo acid catalyzed rearrangement to form (iii) and (iv). Subsequent hydrogenation of the intermediates would produce amine 70. The \triangle^{7-8} double bond and the C-18 NO_2 would resist hydrogenation as in the case of nitroacetate 400.

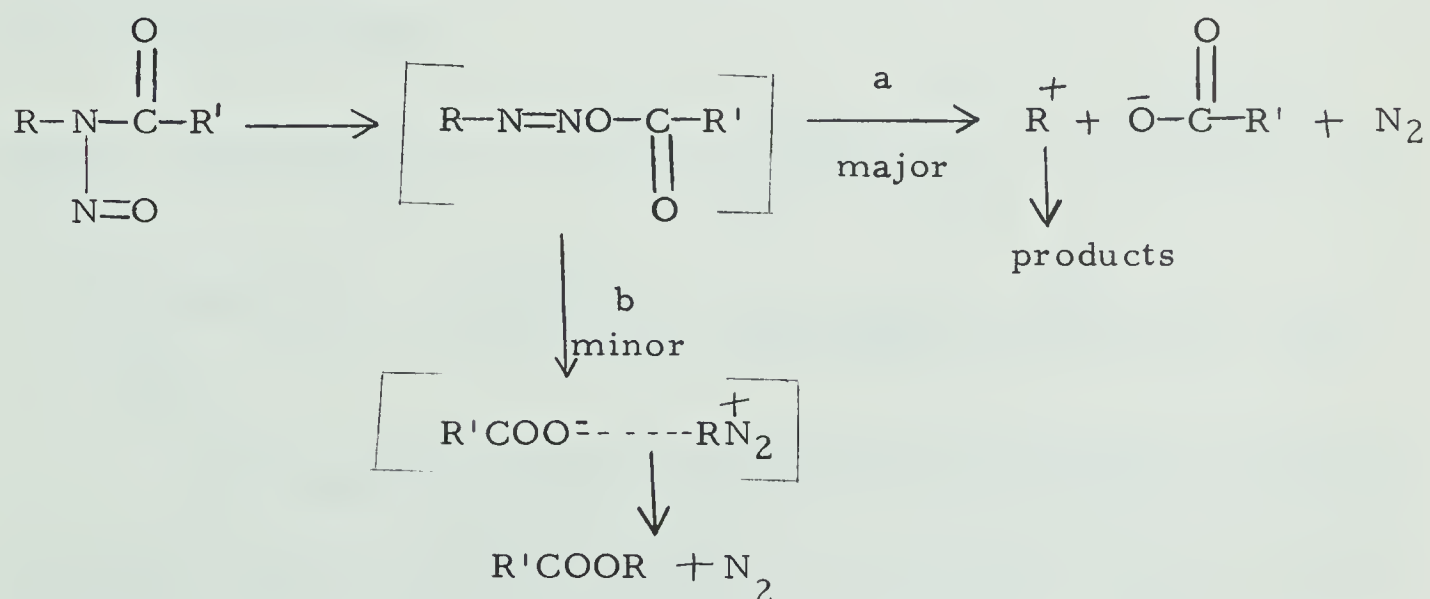
The discussion of the structural elucidation of the dinitro compound 61 will be concluded with a brief account of two abortive attempts made to obtain further evidence in support of the assigned structure.

The first of these, involving pyrolysis⁵⁶ of a nitroso derivative of N-acetate I was directed towards obtaining olefin 71 and/or acetate 72 each of which could potentially be transformed into the known compound





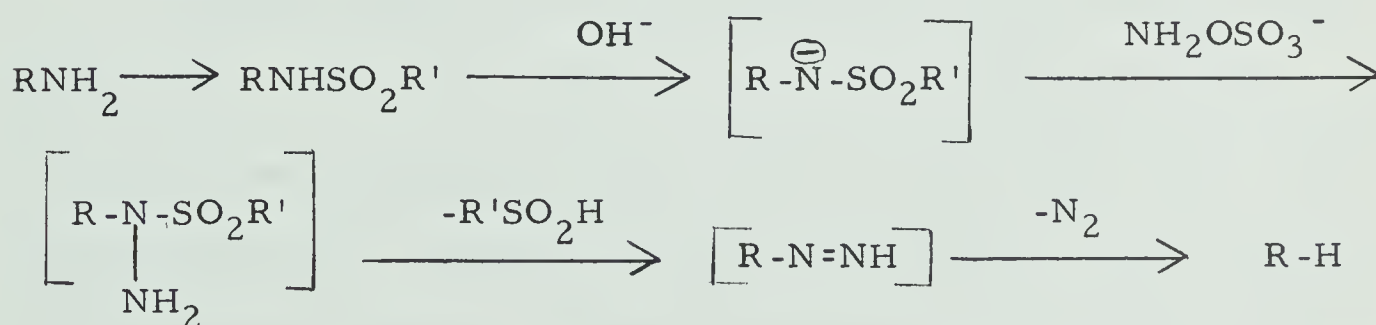
84a (see Chapter III). Conversion of N-nitrosoamides to esters is reported⁴¹ to occur most efficiently (>80%) when the amide function is attached to a primary carbon atom. If, however, such functions are attached to secondary or tertiary carbon atoms the yields of esters are low and products derived from intermediate carbonium ions predominate as indicated below. It was hoped that N-acetate I would lead to a



mixture of 71 and 72 on pyrolysis of its nitroso derivative. Following the method of Ireland et al⁵⁷ an acetic acid solution of N-acetate I was treated with an excess of dinitrogen tetroxide (in HOAc) in the presence

of fused sodium acetate. The product obtained was a complex mixture as determined by t.l.c. and spectrometric methods. With the view to isolating the major components the mixture was subjected to chromatography on alumina. This afforded a small amount of unchanged N-acetate I. The remainder of the material recovered from the chromatography was intractable.

The second method involved attempted transformation of sulfonamide I to compound 84a by reductive deamination. Nickon *et al*⁵⁸ have converted several amino compounds into the corresponding hydrocarbons by this procedure. The first step in this reductive deamination involves preparation of the sulfonamide from the amine. The sulfonamide is then treated with hydroxylamine O-sulfonic acid under alkaline conditions to give the deaminated product. The reaction is believed to proceed by the pathway indicated.

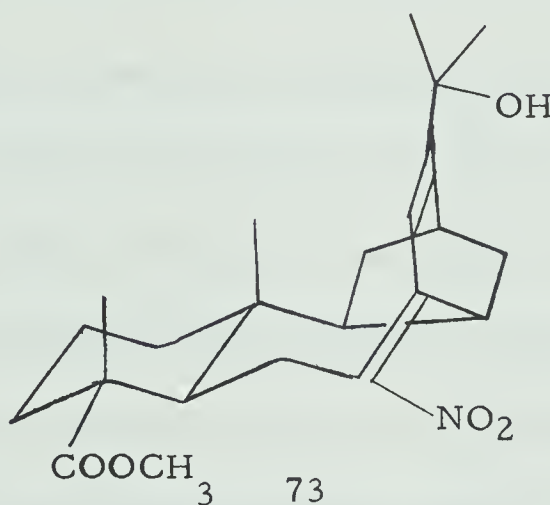


Following the procedure of Nickon⁵⁸ hydroxylamine O-sulfonic acid was added to an alkaline solution of sulfonamide I and the reaction mixture then heated on the steam bath for 22 hours. The product obtained after work-up appeared to have the sulfonamido group unaffected as indicated by its infrared spectrum. The spectrum showed absorption

characteristic of a carboxyl group formed by hydrolysis of the C-1 carbomethoxyl. On treatment with ethereal diazomethane the product gave starting sulfonamide in quantitative yield. Modifications in the reaction conditions involving use of NaOMe-MeOH and KOtBu-tBuOH were also not successful, and gave unchanged sulfonamide.

Nitroalcohol 73

The so-called nitroalcohol is assigned structure 73 on the basis of the following evidence.



The mass spectrum of the nitroalcohol showed a parent peak at m/e 403. Exact mass measurement on this peak revealed its composition as $C_{23}H_{33}NO_5$ (Found, 403.2773, Calc. 403.2759). The nitroalcohol shows a marked similarity to the dinitro compound 61 in other spectral properties. Table V summarizes the relevant data. The presence of a conjugated nitrodiene in the nitroalcohol is inferred by analogy with the dinitro compound. The compounds differ mainly in two respects. The infrared spectrum of the dinitro compound shows a band at 1545 cm^{-1} attributable to a nitro group on a saturated carbon atom whereas the infrared spectrum of nitroalcohol contains a band at

TABLE V

	IR cm ⁻¹	UV mμ(ε _{max})	NMR (τ values)				
			C-12 Me	C-1 Me	C-1 COOMe	C-8 H	C-18 Me
Dinitro compound 61	1320, 1500, 1615, 1725, 1545	229 (6750) 348 (6190)	9.32	8.54	6.32	2.80	8.24, 8.20
Nitro- alcohol 73	1320, 1500, 1610, 1720, 3590	236 (6520) 362 (5560)	9.35	8.58	6.28	2.82	8.58, 8.53

3590 cm⁻¹ indicative of the presence of a hydroxyl group. In the n.m.r. spectra the C-18 methyl groups in the dinitro compound appear at τ 8.24 and τ 8.20 while in the nitroalcohol they appear at τ 8.58 and τ 8.53. The similarity in most of their spectral properties suggests that the two compounds have a close structural relationship. The difference can be rationalized if it is assumed that except for the substituents on C-18 the two compounds are structurally identical. It thus appeared that the C-18 nitro group of the dinitro compound is replaced by a hydroxyl group in the nitroalcohol. The higher field positions of the C-18 methyls (τ 8.58 and τ 8.53) in the nitroalcohol fit nicely into this scheme (e.g., (CH₃)₂CHNO₂, τ 8.45, (CH₃)₂CHOH, τ 8.80).

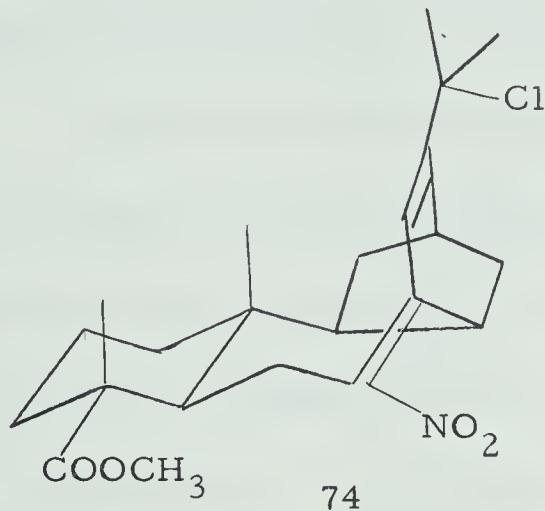
A correlation between the dinitro compound and the nitroalcohol was established in the following manner. An ethanolic solution of the nitroalcohol was acidified with a few drops of conc. HCl and subjected to catalytic hydrogenation over Adam's catalyst at room temperature and at atmospheric pressure. The hydrogenation product was acetylated

with acetic anhydride in the presence of pyridine. The material thus obtained was subjected to chromatography on alumina and N-acetate I (63) was isolated.

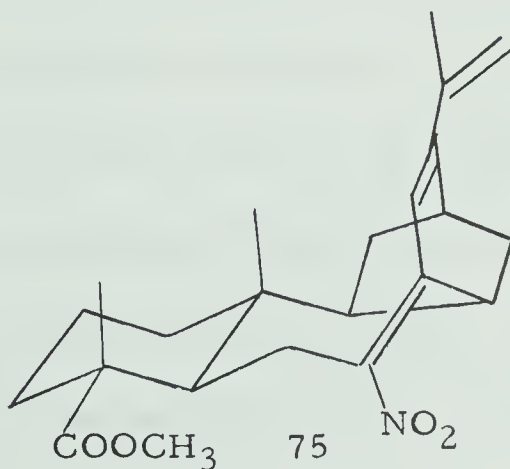
With the correlation between dinitro compound and nitroalcohol established, we turned our attention to dehydration of the alcohol. It may be recalled that the attempts made to extend the conjugated nitro-diene system in the dinitro compound to a conjugated nitrotriene system by pyrolytic elimination of HNO_2 were unsuccessful. The importance of obtaining the conjugated nitrotriene system lay in the fact that its formation would support the location of the nitrodiene chromophore relative to the isopropyl group. Elimination of water from the nitroalcohol was expected to occur with less complication than elimination of nitrous acid from the dinitro compound. Accordingly a solution of nitroalcohol in methylene chloride was treated with thionyl chloride for a period of 18 hours. The product obtained after removal of excess thionyl chloride and solvent showed no absorption in the $3500\text{-}3600\text{ cm}^{-1}$ region of the infrared indicating that the hydroxyl group had been removed. This is further supported by the mass spectrum which does not show a peak at m/e 403 attributable to the molecular ion of the nitroalcohol. A conjugated nitro group in the product was indicated by bands at 1610 cm^{-1} ($\text{C}=\text{C}$), 1500 cm^{-1} , and 1320 cm^{-1} . The ultraviolet spectrum, however, indicated that a conjugated nitrotriene had not been formed since it showed absorption at $237\text{ m}\mu$ and $357\text{ m}\mu$, not much different

from that of the parent nitroalcohol. The n.m.r. spectrum showed the C-1 carbomethoxyl at τ 6.29 and a single olefinic proton at τ 2.87. The retention of all four C-methyls was also apparent. Two of these appear at τ 9.33 and τ 8.51 and can be assigned to the C-12 methyl and the C-1 methyl respectively by analogy with the parent compound. The remaining two methyl groups (C-18) resonated at τ 8.23 and τ 8.17, which suggested that either C-18 is unsaturated or that it bears a strongly electron withdrawing group other than OH. The presence of an isopropylidene group in the thionyl chloride reaction product is difficult to rationalize in terms of the structures we have proposed. Since the spectral properties of this product were similar to those of the dinitro compound and the nitroalcohol the possibility that a skeletal rearrangement had occurred during the reaction appeared remote. It was definitely ruled out in the following manner. The product obtained from thionyl chloride treatment was subjected to catalytic hydrogenation in ethanol over Adam's catalyst. The hydrogenation product was acetylated ($\text{Ac}_2\text{O/py}$) and then chromatographed on alumina. This procedure gave a crystalline compound found to be identical in all respects with N-acetate I. The facts presented thus far are accommodated by the assumption that displacement⁵⁹ rather than elimination had occurred during thionyl chloride treatment. The presence of a chlorine atom was indicated by the mass spectrum which shows peaks at m/e 36 and 38 (H^{35}Cl^+ and H^{37}Cl^+) in approximately 3:1 ratio. Elemental

analysis confirmed the presence of a chlorine atom. Thus, we propose structure 74 for the product obtained from the nitroalcohol by reaction with thionyl chloride.



Acid-catalyzed dehydration of the nitroalcohol was effected successfully. A benzene solution of the nitroalcohol was refluxed in the presence of a catalytic amount of p-toluenesulfonic acid⁶⁰ for one hour. During this time the original greenish yellow color of the reaction mixture changed to lemon yellow. The product obtained from the reaction shows properties consistent with the expected structure 75.



The mass spectrum gave a molecular ion at m/e 385 (w). The vinylic nitro group was characterized by absorption at 1320 cm^{-1} (s) and 1500 cm^{-1} (m) in the infrared. The presence of conjugated double bonds is indicated by the weak bands at 1600 cm^{-1} and 1620 cm^{-1} and

absorption characteristic of a terminal methylene appears at 900 cm^{-1} (s). Confirmation of the presence of a nitrotriene system in 75 comes from the u.v. spectrum which shows absorption at $258\text{ m}\mu$ ($\epsilon_{\text{max}} 6270$) and $382\text{ m}\mu$ ($\epsilon_{\text{max}} 5450$). In agreement with the proposed structure the n.m.r. spectrum of compound 75 shows the presence of three olefinic protons. The chemical shift of the C-8 proton ($\tau 2.77$) is nearly the same as in the parent nitroalcohol. Signals at $\tau 4.80$ (relatively broad) and $\tau 4.59$ are attributed to the protons on the terminal methylene group. Consistent with its location on unsaturated carbon the methyl group on C-18 gives a signal at $\tau 8.00$. The other methyl groups appear at $\tau 9.34$ (C-12 methyl) and $\tau 8.50$ (C-1 methyl).

Attempted crystallization of 75 from hot ethanol led to decomposition of the compound and the formation of an intractable mixture of products. The formation of compound 75 confirms the relative position of the conjugated nitrodiene system in the structure proposed for nitroalcohol. Since correlation between the nitroalcohol and the dinitro compound has been established this evidence becomes complementary in the structural assignment for the latter compound. In view of the structural relationship between the dinitro compound and the trinitro compound, the structure proposed for the latter may now be taken as reasonably well established.

In retrospect, the behaviour of amine 29 ($R = \text{CH}_3$) in nitrous acid deamination seems markedly different from that of the model compound 27. The latter is reported to give alcohol 28 possessing a

rearranged skeleton in ca. 65% yield while amine 29 furnishes a variety of products in this reaction. Some of these products, as we have seen, possess the unrearranged bicyclo[2.2.2]octane system while others have the rearranged skeleton containing bicyclo[3.2.1]octane system. One of the objectives in undertaking this investigation was to test in the laboratory the validity of the postulated biogenetic transformation of the atisine type alkaloids into the lycoctonine type alkaloids. The isolation of products having the rearranged skeleton provides some support for this hypothesis. From the point of view of synthetic utility, however, deamination of amine 29 does not seem promising since a large number of products, rather cumbersome to isolate, is formed. Furthermore these products show many unexpected structural features. These aspects will be considered at greater length in the last chapter of this thesis. Results of the solvolytic approach to the investigation will be discussed next.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating infrared spectrophotometer or a Perkin-Elmer Model 337 grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured in deuteriochloroform, unless otherwise stated, using a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 or HA-100 spectrometer with tetramethylsilane as an internal standard. Spin decoupling experiments were carried out using the latter models. These measurements were carried out by Mr. R. N. Swindlehurst and Mr. G. Bigam and their associates.

Mass spectra were recorded by Dr. A. Hogg and his associates on an A.E.I. Model MS-2H or an A. E. I. Model MS-9 mass spectrometer.

Ultraviolet spectra were measured, unless otherwise specified, in 95% ethanol using a Cary recording spectrometer Model 14M or a Perkin-Elmer Model 202.

Optical rotatory dispersion spectra were measured on a Rudolph Automatic Recording Spectropolarimeter.

Melting points were determined on a hot stage Fisher-Johns melting point apparatus and are uncorrected.

Skellysolve B refers to Skelly Oil Company light petroleum, b.p. 62-70°.

Alumina, unless otherwise specified, means basic alumina of activity III-IV (Brockman Scale).

Microanalyses are by F. Pascher, Bonn, Germany; C. Daessle, Montreal, Quebec; or T. Gygli, Toronto, Ontario.

PREPARATION OF THE ADDUCT 31 ($R = CH_3$).

Levopimaric acid was prepared by the method of Lawrence (J. Am. Chem. Soc. 77, 6311, 1955), and methyl levopimarate was obtained by treatment of levopimaric acid with ethereal diazomethane.

A solution of methyl levopimarate (10 g, 32 mmoles) and acrylic acid (20 ml) in benzene (50 ml) was refluxed on the steam bath for 9 hours. The solution was concentrated under reduced pressure and the brown gummy residue steamsparged for one hour. The white mass which settled at the bottom was separated from the aqueous layer by decantation and dissolved in ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a white solid (12 g). This solid was dissolved in acetone (60 ml) and to the acetone solution was added cyclohexylamine (4.5 ml in 10 ml of acetone). Immediately upon addition of the amine a white salt precipitated. The salt was transferred to a Buchner funnel, washed with acetone and dried to obtain 10 g of a white product. A suspension of this product in ether (200 ml) was shaken with 5% H_3PO_4 (100 ml). The aqueous acidic layer was removed and the ether solution

washed with water (3 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to obtain adduct 31 (7.8 g, 20 mmoles, 62.5%). A sample recrystallized from Skellysolve B melted at 166-167°. Calc. for $C_{24}H_{36}O_4$: C, 74.23; H, 9.28%. Found: C, 74.53; 74.87; H, 9.57, 9.10%. Infrared spectrum: $\int_{\max}^{CCl_4}$ 3200-2400 (br.), 1720 (s), 1700 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.38 (3H), 8.95 (6H, d., $J \approx 7$ c.p.s.), 8.83 (3H), 6.28 (3H), 4.57 (1H), -0.95 (1H, br. s.).

Esterification with ethereal diazomethane gave the ester 34. A sample crystallized from MeOH-H₂O afforded long needles which melted at 65-66°. Mixture melting point with an authentic sample of 34 was undepressed. The infrared spectrum of 34 was superimposable upon that of an authentic sample. Nuclear magnetic resonance spectrum: τ 9.37 (3H), 8.94 (6H, d., $J \approx 7$ c.p.s.), 8.84 (3H), 6.45 (3H), 6.35 (3H), 4.67 (1H). Mass spectrum*: m/e 402 (molecular ion, 26), 316 (71), 146 (100), 133 (72), 121 (88), 101 (62), 91 (88).

REACTION OF ADDUCT 31 (R = CH₃) WITH LEAD TETRAACETATE.

a) Reaction of adduct 31 (R = CH₃) with lead tetraacetate.

Adduct 31 (4 g, 10.3 mmoles) was dissolved in glacial acetic acid (40 ml) contained in a 100 ml flask protected with a calcium chloride guard tube. To this solution was added acetic anhydride (1 ml)

* Figures in brackets refer to the intensity of the peak as a percentage of the most intense peak.

followed by lead tetraacetate (5.32 g, 12 mmoles). The reaction mixture turned brown. The flask was then placed in an oil bath and the temperature raised to 80°. Sodium acetate (1.3 g), followed by more lead tetraacetate (5.3 g) was added, the temperature raised to 90° and maintained there for one hour. The flask was allowed to cool and stand at room temperature overnight. Excess reagent was destroyed by the addition of ethylene glycol (3 ml) and the solvent removed (55°) under reduced pressure. The residue was extracted with ether (4 x 40 ml) and the extract washed with water followed by 1N HCl (2 x 50 ml). After removal (NaOH) of the unchanged adduct the ether solution was then washed with water, dried over anhydrous sodium sulfate, and evaporated to afford a white foam (3.56 g, 89%). This product possessed the following spectral characteristics. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1775 (s), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.28, 9.12, 9.08, 9.04, 8.87, 8.84, 8.26, 8.22, 6.38, 5.37, 5.17 (underlined signals relatively prominent).

b) Chromatography of the Product on Acid Washed Alumina.

The product (2 g) was chromatographed over acid washed alumina (75 g). Elution with benzene (400 ml) gave 31 mg of material which showed no lactone absorption in the infrared. Elution with benzene-ether (19:1, 300 ml) gave 73 mg of material which showed absorption at 1800 (s) and 1750 cm^{-1} (s) in the infrared. Elution with benzene-ether (3:1, 400 ml) gave an oil (403 mg) which on crystallization

from Skellysolve B afforded 105 mg of compound I (=35). Rechromatography of the noncrystalline residue furnished another 52 mg of compound I (=35). A sample recrystallized from Skellysolve B melted at 147-148° and that recrystallized from methanol at 139-140°. It was found to be identical with an authentic sample of 35 by melting point, mixture melting point and infrared comparison. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CCl}_4}$ 1775 (s), 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.14 (3H, d., $J \approx 8$ c.p.s.), 9.04 (3H), 8.93 (3H, d., $J \approx 7$ c.p.s.), 8.79 (3H), 6.34 (3H), 5.28 (1H). Mass spectrum: m/e 386 (molecular ion, 14), 342 (35), 327 (42), 239 (66), 131 (67), 121 (100), 91 (81). Further elution with benzen-ether (3:1, 400 mls) gave 99 mg of material, which on crystallization from methanol gave 14 mg. of isopropenyl lactone 37, m.p. 170-176°. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CCl}_4}$ 3080 (w), 1775 (s), 1720 (s), 1640 (w), 890 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.07 (3H), 8.79 (3H), 8.23 (3H, slightly br. s.), 6.33 (3H), 5.34 (1H, d., $J \approx 6$ c.p.s.), 5.24 (1H, br. s.), 5.12 (1H, d, $J \approx 1$ c.p.s.). The signal at τ 5.34 collapsed to a singlet on simultaneous irradiation 223 c.p.s. downfield from TMS and the signal at τ 8.23 sharpened on simultaneous irradiation 488 c.p.s. downfield from TMS. The infrared spectrum of the material from the mother liquors was similar to that of the crystalline material.

Further elution with benzene-ether (1:1, 200 ml), ether (300 ml), ether-chloroform (7:3, 200 ml) and chloroform (400 ml) gave 327 mg

of intractable material. Elution with chloroform-methanol (39:1, 200 ml), and chloroform-methanol (19:1, 100 ml) afforded 19 mg of a solid which on crystallization from ether gave compound III (27 mg), m.p. 207-211^o. Infrared spectrum: $\int_{\max}^{\text{nujol}}$ 3500-2400 (broad), 1750 (s, broad), 1715 cm⁻¹ (s). Nuclear magnetic resonance spectrum: τ 9.09 (3H), 8.78 (3H), 8.70 (3H, d., $J \approx 4$ c.p.s.), 7.58 (1.5 - 2H, br. absorption), 6.45 (2H, m.), 6.33 (3H, s), 5.3 (1H, d. of d. $J \approx 5$ and 3.5 c.p.s.). Exchange with D₂O caused the signal at τ 7.58 to disappear. The signal at τ 5.30 collapsed to a doublet ($J \approx 3.5$ c.p.s.) on simultaneous irradiation 196 c.p.s. downfield from TMS. Mass spectrum: m/e 389 (59), 371 (52), 346 (35), 121 (91), 107 (98), 106 (100). Continued elution with chloroform-methanol (19:1, 300 ml) gave a white foam (282 mg) which showed absorption at 3200-2400 (broad), 1780 (m), 1720 (s), 1700 (s), 1665 (sh), 1670 cm⁻¹ (w) in the infrared spectrum (CCl₄). Elution with methanol-acetic acid (49:1, 200 ml) gave a gum (488 mg) which on crystallization from Skellysolve-benzene afforded 82 mg of compound IV (38). Recrystallization from acetonitrile gave the analytical sample, m.p. 163-166^o. Calc. for C₂₄H₃₄O₄: C, 74.61; H, 8.81%. Found*: C, 73.80; H, 8.14, N, 0.64%. Infrared spectrum: $\int_{\max}^{\text{CCl}_4}$ 3200-2400 (broad), 1720 (s), 1700 (s), 1665 (sh.), 1620 (w) 880 cm⁻¹ (m). Nuclear magnetic resonance spectrum: τ 9.43 (3H), 8.83 (3H), 8.08 (3H), 5.25 (1H),

* This sample probably contains some acetonitrile.

4.99 (1H); 4.15 (1H). Ultraviolet spectrum: λ_{\max} 242 m μ (26,400). Esterification with ethereal diazomethane gave the corresponding methyl ester which possessed the following spectral properties. Infrared spectrum: $\nu_{\max}^{\text{CCl}_4}$ 3100 (w), 1730 (s), 1670 (w), 1625 (w), 885 cm^{-1} (m). Mass spectrum: m/e 400 (molecular ion, 10), 325 (23), 314 (23), 159 (48), 131 (67), 121 (100), 117 (74), 91 (60), 55 (61).

The noncrystalline residues from the last two fractions were combined. The infrared spectrum of the material changed after a few days; the band at 1775 cm^{-1} became much stronger and the one at 1700 cm^{-1} became less intense. This material (615 mg) was chromatographed on silica gel (30 g). Elution with benzene (150 ml) and benzene-ether (19:1, 400 ml) gave 325 mg of material, which on crystallization from methanol provided colorless plates of compound V (\approx 39), m.p. 191-192 $^{\circ}$. Infrared spectrum: $\nu_{\max}^{\text{CCl}_4}$ 1770 (s), 1720 (s), 1670 (w), 960 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.28 (3H), 8.83 (3H), 8.25 (3H), 8.21 (3H), 6.32 (3H), 4.99 (1H).

A solution of the isopropylidene lactone 39 (110 mg) in glacial acetic acid (30 ml) was hydrogenated over Adam's catalyst (36 mg) at 65-70 $^{\circ}$ and 50 p.s.i.. After 24 hours the solution was filtered and the solvent removed under reduced pressure. The residue was taken up in ether, the ether solution extracted with 10% Na_2CO_3 (2 x 25 ml) and washed with water (2 x 25 ml). The alkaline extract and the washings were combined, acidified with dilute HCl and extracted with

ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to afford 60 mg of a white solid.

This was found to be mainly adduct 31 ($R = CH_3$) from n.m.r. and t.l.c. comparison with an authentic sample.

c) Chromatography on Silica Gel.

The neutral products from the lead tetraacetate oxidation (1.345 g) were chromatographed on silica gel (80 g of BDH). 10 ml fractions were collected using an automatic fraction collector. Fractions 1-30, eluted with benzene (250 ml) and benzene-ether (99:1, 50 ml) gave 46 mg of an oil. The infrared spectrum showed weak absorption at 1780 cm^{-1} . Fractions 31-43, eluted with benzene-ether (99:1, 130 ml), gave material (65 mg) which showed absorption at 1800 (s), 1720 (s), 1370 cm^{-1} (m) in the infrared. Fractions 44-55, eluted with benzene-ether (99:1, 120 ml) gave 120 mg. of material which on crystallization from Skellysolve B afforded cyclopropyl lactone 35 (75 mg). Fractions 56-64, eluted with benzene-ether (99:1, 90 ml), gave 120 mg of material, which on crystallization from Skellysolve B afforded cyclopropyl lactone 35 (40 mg). The residue was combined with the next fraction. Fractions 65-115, eluted with benzene-ether (99:1, 440 ml) and benzene-ether (39:1, 70 ml) gave 328 mg of material. To this was added the residue from fractions 56-64. Crystallization from methanol afforded the isopropylidene lactone 39 (250 mg). Fractions 116-137, eluted with benzene-ether (39:1, 220 ml) gave intractable

material (60 mg). Fractions 138-175, eluted with benzene-ether (19:1, 380 ml) gave 226 mg of material rich in acetoxy lactone 40. Further elution with solvents including ether, chloroform and chloroform-methanol (7:1) gave intractable material.

The material from fractions 138-175 above was rechromatographed on silica gel (12.5 g). Elution with benzene (100 ml) and benzene-ether (49:1, 100 ml) gave 69 mg of unidentified material. Continued elution with benzene-ether (49:1, 125 ml) gave 106 mg of material which crystallized from ether to give colorless needles of acetoxy lactone 40 (18 mg), m.p. 180-183⁰. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1780 (s), 1720 (s), 1365 cm⁻¹ (m). Nuclear magnetic resonance spectrum: τ 9.09 (3H), 8.78 (3H), 8.39 (6H), 8.03 (3H), 6.34 (3H), 5.40 (1H, d., $J \approx 6$ c.p.s.). The signal at τ 5.40 collapsed to a singlet on simultaneous irradiation 205 c.p.s. down-field from TMS. The mass spectrum showed the ion of highest mass at m/e 386 (M-60).

In another experiment material rich in acetoxy lactone 40, obtained by chromatography on silica gel was rechromatographed on neutral alumina (grade II, Woelm). A small amount of isopropenyl lactone 37 was isolated from the middle fractions eluted with benzene-ether (1:1). Later fractions, eluted with chloroform-acetic acid (19:1) gave material which showed strong absorption at 1580 cm⁻¹ (-COO⁻).

d) Transformation of Lactone 36 to Ketoester 41.

In an earlier experiment a methanolic solution of lactone 36 was subjected to prolonged treatment with sodium methoxide. The solution was then concentrated under reduced pressure, diluted with water and acidified with conc. HCl. The precipitate was extracted with ether, the ether extract was dried over anhydrous magnesium sulfate and evaporated. The product contained both a hydroxy acid and a lactone (IR). The following procedure was therefore followed.

To a solution prepared by dissolving sodium metal (158 mg) in anhydrous methanol (3 ml), followed by addition of dry dimethyl sulfoxide (8 ml), was added lactone 36 (191 mg). The reaction mixture, protected from moisture with a Drierite tube, was heated to 90° for 48 hours and left at room temperature for another 72 hours. The solid, which deposited, was isolated by decantation and washed with methanol to afford 145 mg of a crystalline hydroxy dicarboxylate. A slurry of this salt in dry pyridine (10 ml) was added with stirring to CrO₃-pyridine complex (200 mg of CrO₃ in 5 ml of dry pyridine) at 0°. After one hour of stirring at this temperature the reaction mixture was transferred to the refrigerator overnight. It was then diluted with water (100 ml), acidified with conc. HCl and extracted with chloroform (3 x 60 ml). The chloroform extract was washed with water, dried over anhydrous calcium sulfate and evaporated to give dark brown material (185 mg). This was esterified with ethereal diazomethane.

The ether soluble material thus obtained (128 mg) was sublimed at 140-150° under reduced pressure to afford a colorless solid (63 mg). Crystallization from Skellysolve B furnished needles of ketoester 41, m.p. 174-175°. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1635 cm^{-1} (s); $\nu_{\text{max}}^{\text{nujol}}$ 1740 (s), 1720 (s), 1700 (s), 1625 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.38 (3H), 8.90 (3H), 8.13 (3H), 7.74 (3H), 6.38 (3H), 6.35 (3H). Ultraviolet spectrum: λ_{max} 260 m μ (11,370). Mass spectrum: m/e 416 (molecular ion, 100), 401 (26), 356 (40), 316 (66), 235 (64), 91 (73), 55 (68).

TRANSFORMATION OF ADDUCT 31 (R=CH₃) TO THE AMINE 29 (R=CH₃).

a) Attempted Conversion of Adduct 31 to Amine 29 by the Schmidt Reaction.

i) Isolation of Lactam 42.

To a solution of adduct 31 (1.94 g, 5 mmoles) in chloroform (25 ml) was added a solution of hydrazoic acid (10 ml) in the same solvent. The resulting solution was warmed to 40° and concentrated sulfuric acid (3 ml) was added with stirring over a period of 2 $\frac{1}{2}$ hours. The reaction mixture was then diluted with water (40 ml). The chloroform layer was removed, washed with water, dried over anhydrous sodium sulfate and evaporated to give the nonbasic product (1.41 g, 72%). The aqueous acidic layer was basified with dilute sodium carbonate and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate and evaporated to give the basic product

(0.215 g, 11%). The nonbasic product possessed the following spectral characteristics. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CCl}_4}$ 3440 (w), 3220 (w, broad), 2800-2400 (broad), 1775 (w), 1725-1700 (s, broad), 1650 cm^{-1} (sh.).

Treatment of the nonbasic product with ethereal diazomethane gave material which showed absorption at 3440 (w), 3220 (H), 1720 (s), 1700 cm^{-1} (s) in the infrared. This material (910 mg) was subjected to chromatography on silica gel (36 g). Elution with benzene (100 ml) gave material (298 mg) which showed absorption at 1780 cm^{-1} (w, γ lactone) in the infrared. Continued elution with benzene-ether (1:1, 200 ml) gave a white foam (421 mg) which on crystallization from methanol afforded colorless plates of lactam 42 (143 mg), m.p. 237 - 238°. Calcd. for $\text{C}_{24}\text{H}_{35}\text{NO}_3$: C, 74.80; H, 9.09; N, 3.63%.

Found: C, 74.63, 74.32; H, 9.30, 9.20; N, 3.55%. Infrared spectrum: $\bigvee_{\text{max}}^{\text{nujol}}$ 3360 (s), 1705 (s), 1690 (s), 1260 cm^{-1} (s).

Nuclear magnetic resonance spectrum: τ 9.21 (3H), 8.85 (3H), 8.33 (3H), 8.18 (3H), 7.25-6.80 (3H), 6.34 (3H), 3.86 (1H, broad s.).

ii) Attempted Hydrolysis of Lactam 42 with Concentrated Hydrochloric Acid.

Lactam 42 (86 mg) was refluxed in constant boiling hydrochloric acid (10 ml) for 46 hours. The solution was then evaporated on the steam bath. The white residue thus obtained (101 mg) possessed the following spectral properties. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 3200-2400 (broad), 1725 (s), 1690 (s), 1605 (w), 1510 cm^{-1} (m). The n.m.r.

spectrum was poorly resolved. The material was treated with ethereal diazomethane and then crystallized from methanol to give colorless needles, m.p. 276-285°. Elemental analysis; Found:

C, 72.47; H, 9.28; N, 2.66; O, 16.16%. Infrared spectrum:

$\nu_{\text{max}}^{\text{CHCl}_3}$ 3440 (m), 1715 (s), 1685 (s), 1250 cm^{-1} (s). Nuclear

magnetic resonance spectrum: τ 9.02 (3H), 8.83 (6H, d., $J \approx 7$ c.p.s.), 8.72 (3H), 7.18 (≈ 2 H), 6.31 (3H), 3.45 (≈ 1 H, br. s.).

iii) Attempted Opening of Lactam 42 via Iminoether.

To a solution of triethyloxonium fluoborate (165 mg) in methylene chloride (2 ml) was added a solution of lactam 42 (102 mg) in the same solvent (3 ml). The reaction mixture, protected from moisture with a calcium chloride tube, was stirred overnight. Dilute potassium carbonate (10%, 20 ml) was then added and the product extracted with methylene chloride (4 x 20 ml). The methylene chloride extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give iminoether (43) (91 mg). Infrared spectrum:

$\nu_{\text{max}}^{\text{CHCl}_3}$ 1710 (s), 1640 (s), 1370 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.27 (3H), 8.88 (3H), 8.80 (3H, t., $J \approx 7$ c.p.s.), 8.42 (3H), 8.37 (3H), 7.40-6.70 (3H), 6.48 (3H), 6.00 (2H, d., $J \approx 7$ c.p.s.).

A solution of the above iminoether in 10% acetic acid in aqueous dioxane (1:1, 20 ml) was refluxed for four hours and then left at room temperature overnight. Most of the solvent was evaporated on the rotary evaporator and the residue taken up in ether (40 ml). The

ether solution was washed with 10% sodium carbonate (10 ml) followed by water (2 x 10 ml). It was then dried over anhydrous magnesium sulfate, filtered and evaporated to give 86 mg of the starting lactam.

Hydrolysis of iminoether 43 with 1N sulfuric acid in aqueous dioxane (1:1) also gave the starting lactam.

iv) Formation of Lactam 42 from Isocyanate 47.

To a solution (40^o) of isocyanate 47 (540 mg) in chloroform (25 ml) was added dropwise with stirring concentrated sulfuric acid (1.5 ml). The reaction mixture was then diluted with water (50 ml) and extracted with chloroform (50 ml). The chloroform extract was washed with water, dried over anhydrous sodium sulfate and evaporated to give a white foam (537 mg). This was treated with ethereal diazomethane and the product thus obtained subjected to chromatography on silica gel. Early fractions, eluted with benzene, gave a small amount of an unidentified oil. Fractions eluted with benzene-ether (1:1, 200 ml) gave material (72 mg) which crystallized from methanol to afford lactam 42 identical in all respects with an authentic sample.

An alternative method for the preparation of lactam 42 from isocyanate 47 is as follows.

A concentrated solution of isocyanate 47 (3.6 g) in benzene was adsorbed on a column of silica gel (120 g). Elution with benzene (200 ml), benzene-ether (3:1, 100 ml), ether (100 ml) and ether-chloroform (1:1, 50 ml) gave unchanged isocyanate 47 (2.4 g). Elution with chloro-

form (200 ml) and chloroform-methanol (9:1, 200 ml) gave material (330 mg) which was a mixture of isocyanate and lactam (IR). Elution with chloroform-methanol (4:1, 200 ml) gave material (800 mg), which crystallized from methanol to afford colorless plates of lactam 42.

b) Attempted Transformation of Adduct 31 ($R=CH_3$) to amine 29 ($R=CH_3$) by the Curtius Reaction.

i) Preparation of Isocyanate 47.

A solution of adduct 31 (10 g) and thionyl chloride (5 ml) in dry benzene (100 ml) was refluxed for 5 hours. The solvent was evaporated under reduced pressure and the residue subjected to repeated co-distillation with benzene (6 x 50 ml) to remove excess of thionyl chloride. Traces of the solvent were removed on the vacuum pump to obtain 46a as a dark brown gum. Infrared spectrum: $\nu_{\max}^{CCl_4}$ 1800 (s), 1720 cm^{-1} (s). To a cooled ($5-10^\circ$) solution of acid chloride 46a (≈ 10 g) in acetone (100 ml) was added with stirring an aqueous solution of sodium azide (2 g in 6 ml of H_2O) over a period of one hour. After continued stirring for another hour at this temperature the reaction mixture was allowed to warm to room temperature and stand for two hours. The reaction mixture was diluted with water (100 ml), when a brown colored oil separated and settled at the bottom of the flask. The supernatant aqueous layer was removed by decantation and the oil dissolved in benzene (50 ml). Evaporation of the benzene solution under reduced pressure gave a dark brown mass which contained traces of water.

These were removed by azeotropic distillation with benzene on the rotary evaporator. The product thus obtained showed absorption at 2260 (s), 2140 (s), 1720 cm^{-1} (s) in the infrared (CCl_4). It was dissolved in dry benzene (60 ml) and the solution refluxed for $3\frac{1}{2}$ hours. Removal of the solvent under reduced pressure afforded isocyanate 47 as a dark brown foam. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 2260 (v.s.), 1720 cm^{-1} (s).

ii) Hydrolysis of Isocyanate 47 under Alkaline Conditions.

A suspension of isocyanate 47 (720 mg) in benzene (10 ml) containing 50% aqueous potassium hydroxide (10 ml) was heated to reflux for 2 hours and then left at room temperature overnight. Benzene (25 ml) was added and the aqueous alkaline layer separated. The benzene layer was extracted with dilute hydrochloric acid (25 ml), washed with water, dried over anhydrous magnesium sulfate and evaporated to give nonbasic material (656 mg, 91%). The acidic extract and the washings were combined, basified with sodium carbonate and extracted with ether. The ether extract gave 15 mg (2%) of basic product. A portion (265 mg) of the nonbasic material was chromatographed on silica gel (14 g). The middle fractions eluted with benzene-ether (1:1, 50 ml) gave material (\approx 150 mg) which crystallized from methanol as colorless needles, believed to be the symurea 48 (13 mg), m.p. $158-161^\circ$.

Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 3440 (m), 1720 (s), 1670 (s), 1500 cm^{-1} (m).

iii) Hydrolysis of Isocyanate 47 under Acidic Conditions.

A solution of isocyanate 47 (1.018 g) in dimethoxyethane (40 ml) containing concentrated hydrochloric acid (25 ml) was heated to reflux for 3 hours. The acid was then neutralized with sodium carbonate and the solvent evaporated under reduced pressure. The residue was taken up in ether, the ether solution extracted with dilute hydrochloric acid, washed with water, dried and evaporated to give non-basic material (610 mg). The acidic extract and the washings were basified with sodium carbonate and extracted with ether to afford 174 mg (17%) of basic product. The nonbasic product on crystallization from methanol gave a crystalline substance (78 mg) found to be identical in all respects with lactam 42. The basic product was found to be identical by infrared and t.l.c. comparison with amine 29 ($R=CH_3$) obtained by hydrolysis of the N-formyl compound 49.

c) Preparation of Amine 29 ($R=CH_3$) from Isocyanate 47 by Hydride Reduction - Hydrolysis Sequence.

A solution of isocyanate 47 (10 g) in dimethoxyethane (60 ml) was added with stirring to a slurry of sodium borohydride (2.5 g) in dimethoxyethane (400 ml). After continued stirring for 24 hours the solvent was evaporated on the rotary evaporator and the residue treated with dilute hydrochloric acid (1N, 120 ml). The product was then extracted with ether (350 ml). The ether extract was washed with water (2 x 100 ml), dried over anhydrous magnesium sulfate and

evaporated to give the N-formyl compound 49 (≈ 10 g) as a white foam.

Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 3435 (m), 3400 (w), 1715 (s), 1680 (v.s.),

1235 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.36 (3H),

8.97 (6H, d., $J \approx 6$ c.p.s.), 8.86 (3H), 6.36 (3H), 4.8-4.3 (2H, a

broad signal for N-H overlaps a sharp singlet at τ 4.67), 1.96 (1H).

The N-formyl compound was used without further purification in the

next step. The N-formyl compound 49 (≈ 10 g) was refluxed in

ethanolic hydrochloric acid (3:1, 280 ml) on the steam bath for 5 hours.

The acidic solution was diluted with water (50 ml) and neutralized with

sodium carbonate. Most of the solvent was then removed on the

rotary evaporator. To the residue was added water (200 ml) and

ether (300 ml) and the three phase mixture was transferred to a

separatory funnel. The aqueous alkaline layer and the white precipitate

floating at the interface of the two layers were removed. The ether

layer was extracted with 1N hydrochloric acid (50 ml), washed with

water (2 x 50 ml), again extracted with 1N hydrochloric acid (50 ml)

and washed with water. Evaporation of the ether layer gave nonbasic

product (1.7 g). The acidic extract and the washings were combined,

basified with sodium carbonate and extracted with ether (400 ml). The

ether extract was dried over anhydrous magnesium sulfate, filtered

and evaporated to give a viscous oil (7 g). This oil was dissolved in

anhydrous ether (100 ml) and into the cooled (0°) solution was passed

hydrogen chloride. The original colorless solution became brownish

but the hydrochloride did not precipitate. The ether solution was evaporated to give a white foam (7.5 g). This was dissolved in ether (30 ml) and stored in the refrigerator overnight. The precipitated salt was removed by decantation. Two crops gave 6.8 g of amine hydrochloride 50. A sample recrystallized from methyl acetate melted at 210-214^o. Calc. for C₂₃H₃₈NO₂Cl: C, 69.79; H, 9.61; N, 3.54%. Found: C, 68.95, 68.56; H, 9.35, 9.37; N, 3.37%. Infrared spectrum: $\nu_{\text{max}}^{\text{nujol}}$ 3440 (w, broad), 3100-3000 (sh.), 1720 (s), 1600 (w, broad), 1580 (w, broad), 1500 cm⁻¹ (m). Nuclear magnetic resonance spectrum: τ 9.36 (3H), 8.89 (6H, d., J \approx 7 c.p.s.), 8.83 (3H), 6.29 (3H), 4.52 (1H), 2.03 (3H, broad). Basification of an aqueous solution of amine hydrochloride 50 and extraction with ether afforded pure amine 29 (R=CH₃) as viscous oil. Calc. for C₂₃H₃₇NO₂: C, 76.88; H, 10.30; N, 3.90%. Found: C, 77.05, 76.74; H, 10.35, 10.37; N, 3.55%. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 3500-3200 (w, broad), 1720 (s), 1660 (w), 1240 cm⁻¹ (s). Nuclear magnetic resonance spectrum: τ 9.38 (3H), 8.97 (6H, d., J \approx 7 c.p.s.), 8.85 (3H), 6.35 (3H), 4.74 (1H). Mass spectrum: m/e 359 (molecular ion, 1), 344 (7), 316 (59), 133 (65), 121 (92), 91 (100).

DEAMINATION OF AMINE 29 (R = CH₃).

a) Isolation of Products.

i) Deamination in Glacial Acetic Acid.

To a solution of amine hydrochloride 50 (2 g, 5 mmoles) in

glacial acetic acid (16 ml) was added with stirring sodium nitrite (700 mg, 10 mmoles) over a period of 75 minutes. The reaction mixture was kept stirred in a stoppered flask overnight. Next morning more sodium nitrite (350 mg, 5 mmoles) was added and stirring was continued for two hours. An ice-cold solution of sodium hydroxide (12 g in 80 ml of H_2O) was added and the yellow aqueous alkaline layer transferred to a separatory funnel. The brown gummy residue was dissolved in ether (150 ml) and transferred to the separatory funnel. The contents of the separatory funnel were shaken, the aqueous layer was removed and the ether layer washed with water (2 x 50 ml). Unchanged amine 29 was isolated by extracting the ether solution with dilute hydrochloric acid (2 x 50 ml). The ether solution was then washed with water (2 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to give the nonbasic product (1.275 g, 71%). Basification of the hydrochloric acid extract and the acidic washings followed by extraction with ether gave amine 29 (0.35 g, 12%). The nonbasic product was dissolved in ether (5 ml) and stored in the refrigerator overnight. Removal of the supernatant ether solution gave crystalline trinitro compound (203 mg, 12% overall yield). Crystallization from ethanol gave the analytical sample, m.p. $175.5-178^{\circ}$.
Calc. for $C_{23}H_{33}N_3O_8$: C, 57.61; H, 6.94; N, 8.76; O, 26.69%.
Found: C, 57.94, 58.25; H, 7.19, 7.03; N, 8.76; O, 26.00%.
Molecular weight determined osmotically: 509 (CH_2Br_2). Infrared

spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1725 (s), 1570 (v.s.), 1550 (v.s.), 1350 (m), 1325 (m), 1265 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 8.93 (3H), 8.63 (3H), 8.21 (6H), 6.25 (3H), 5.12 (1H, m), 3.90 (1H, br. s.). Under high resolution the signal at τ 3.90 appeared as a poorly resolved quartet ($J \approx 1$ c.p.s. and < 1 c.p.s.). Spin decoupling experiments indicated the coupling of ≈ 1 c.p.s. due to a proton resonating at 256 c.p.s. downfield from TMS and the coupling of < 1 c.p.s. due to a proton resonating at 324 c.p.s. downfield from TMS. Mass spectrum: m/e 433 (M-46, 2), 386 (10), 357 (27), 341 (100), 281 (39), 121 (31), 91 (32). Exact mass measurement on m/e 341 indicated its composition as $\text{C}_{23}\text{H}_{33}\text{O}_2$ (calc. 341.2481; found 341.2485). The noncrystalline residue showed absorption at 1720 (s), 1630 (w), 1540 cm^{-1} (s) in the infrared (CCl_4). Chromatography of this material on alumina provided small amounts of dinitro compounds.

ii) Deamination in Aqueous Acetic Acid.

To a solution of amine 29 (2.67 g, 7.5 mmoles) in aqueous acetic acid (1:1, 30 ml) was added with stirring (mechanical) sodium nitrite (1.03 g, 15 mmoles) over a period of 95 minutes. During the addition the solution became cloudy and eventually an oil separated. After allowing the reaction mixture to stand overnight more sodium nitrite (0.52 g, 7.5 mmoles) was added and stirring was continued for another two hours. The reaction mixture was then subjected to a work-up as in the case of deamination in glacial acetic acid. This gave a non-

basic product (1.5 g, 56%) and the unchanged starting amine 29 (1.0 g, 37%). The nonbasic product showed absorption at 3610 (v.w.), 3500-3400 (w., broad), 1725 (s), 1630 (v.w.), 1540 cm^{-1} (s). It was dissolved in ether and the solution seeded with a crystal of trinitro compound. This gave 20 mg of trinitro compound. The noncrystalline residue was combined with similar material from another experiment (total 2.4 g) and subjected to chromatography on alumina (72 g). Fractions 1-8 eluted with Skellysolve B (200 ml), Skellysolve B-benzene (1:1, 200 ml) and benzene (400 ml) gave an oil (120 mg). Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1720 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.15, 8.83, 8.46, 8.37, 6.34, no signal in the lower field region. Mass spectrum: m/e 342 (ion of highest mass). Fractions 9-11 eluted with benzene-ether (32:1, 300 ml) gave an oil (60 mg). The nuclear magnetic resonance spectrum of this oil showed a signal at τ 7.90 attributable to an acetoxy group. Further investigation of fractions 1-11 was not undertaken.

Fractions 12-21 (rich in dinitro compound) eluted with benzene-ether (32:1, 200 ml), benzene-ether (9:1, 400 ml) and benzene-ether (1:1, 400 ml) gave a yellow foam (301 mg) which crystallized from ethanol on seeding with a crystal of dinitro compound (obtained from the previous experiment after repeated chromatography) to afford 103 mg of yellow needles of 61, m.p. 136-137°. Recrystallization from ethanol gave the analytical sample. Calc. for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_6$: C, 63.87; H, 7.46;

N, 6.48%. Found: C, 63.73, 63.87; H, 7.47, 7.60; N, 6.37, 6.39. Infrared spectrum: $\nu_{\max}^{\text{CHCl}_3}$ 1725 (s), 1615 (m), 1545 (s), 1500 (s), 1320 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.32 (3H), 8.54 (3H), 8.24 (3H), 8.20 (3H), 6.32 (3H), 2.80 (1H). Ultraviolet spectrum: λ_{\max} 348 m μ (6190); 229 m μ (6750). Mass spectrum: m/e 432 (molecular ion, <1), 403 (2), 402 (3), 386 (100), 135 (19), 121 (25), 107 (49), 91 (38). Exact mass measurements: m/e 403 (calc. for $\text{C}_{23}\text{H}_{33}\text{NO}_5$, 403.2359; found: 403.2355), 386 (calc. for $\text{C}_{23}\text{H}_{32}\text{NO}_4$, 386.2331; found: 386.2334). The noncrystalline residue was saved for further investigation.

Fractions 22-25 eluted with ether (200 ml) and ether-chloroform (1:1, 200 ml) gave 56 mg of intractable material.

Fractions 26-27 (early alcohols) eluted with ether-chloroform (1:1, 200 ml) gave material (101 mg) which showed absorption at 3600 cm^{-1} (sharp) in the infrared. This was acetylated with acetic anhydride in pyridine. Crystallization of the acetylated material from methanol afforded colorless needles (18 mg) of acetate 402. Some experiments in which the separation was more efficient afforded acetate 402 in higher yields (70-80 mg). A sample recrystallized from methanol melted at 145-146°. Infrared spectrum: $\nu_{\max}^{\text{CCl}_4}$ 1740-1730 (s, broad), 1380 (m), 1250 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.16 (3H), 8.85 (3H), 8.46 (3H), 8.37 (3H), 8.02 (3H), 8.0-7.5 (3H), 7.36 (1H, m), 6.37 (3H), 5.48 (1H, octet, $J \approx 9, 3.5$ and 1.5 c.p.s.).

Mass spectrum: m/e 402 (molecular ion, < 1), 342 (53), 327 (42), 267 (48), 121 (37), 107 (100). The noncrystalline residue was combined with the material obtained by acetylation of later alcohols.

Fractions 28-35 (later alcohols) eluted with chloroform (800 ml) gave a yellow foam (690 mg) which showed absorption at 3590 (m), 1540 (m), 1500 (s), 1320 cm^{-1} (s) in the infrared. This material was acetylated with acetic anhydride and pyridine. The acetylated material was combined with the noncrystalline residue from the acetylated early alcohols.

Rechromatography of the Noncrystalline Residue from the Fractions Rich in Dinitro Compound.

The noncrystalline residue (206 mg) was chromatographed on neutral alumina (8 g Woelm, grade IV). Fractions 1-3 eluted with Skellysolve B (135 ml) gave an unidentified material (6 mg). Fractions 4-7 eluted with Skellysolve B (180 ml) gave material (26 mg) which on crystallization from methanol afforded acetate 402 (13 mg). Fractions 8-9 eluted with Skellysolve B (45 ml) and Skellysolve B-benzene (9:1, 45 ml) gave 15 mg of intractable material. Fractions 10-14 eluted with Skellysolve B-benzene (9:1, 225 ml) gave material (23 mg) which on crystallization from ethanol afforded dinitro compound (11 mg). Fractions 15-17 eluted with Skellysolve B-benzene (7:3, 135 ml) gave material (30 mg) which showed absorption at 1540 (s), 1370 (m), 1340 cm^{-1} (w) in the infrared, attributable to nitroacetate 400. Fractions

18-24 eluted with Skellysolve B-benzen (7:3, 135 ml) and benzene (180 ml) gave material (51 mg) which was rechromatographed on silica gel to give ketone 316 (14 mg). A sample crystallized from Skellysolve B melted at 132-133^o. Infrared Spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1720 (s), 1670 (s), 1625 cm⁻¹ (m). Nuclear magnetic resonance spectrum: τ 9.18 (3H), 8.77 (3H), 6.33 (3H), 4.38 (3H). Ultraviolet spectrum: λ_{max} 243m μ (11,080). Mass spectrum: m/e: 316 (molecular ion, 100), 301 (12), 257 (43), 181 (15), 136 (85), 121 (78), 91 (34). Exact mass measurement: m/e 316 (calc. for C₂₀H₂₈O₃, 316.2040; found 316.2044).

Rechromatography of Acetylated Alcohols.

The noncrystalline residue from acetylated early alcohols and the material obtained by acetylation of later alcohols were combined, (790 mg) and subjected to chromatography on neutralalumina (26 g, Woelm, grade IV). Fractions 1-9 eluted with Skellysolve B (300 ml) and Skellysolve B-benzene (19:1, 150 ml) gave an unidentified oily material (6 mg). Fractions 10-18 eluted with Skellysolve B-benzene (85:15, 200 ml) gave material (24 mg) which on crystallization from ethanol afforded dinitro compound (5 mg). Fractions 23-25 eluted with Skellysolve B-benzene (1:1) gave material (98 mg) which on trituration in Skellysolve B afforded crystalline nitroacetate 400 (18 mg), m.p. 130-131^o. Recrystallization from ethanol gave the analytical sample. Calc. for C₂₅H₃₇NO₆: C, 67.09; H, 8.33; N, 3.13%.

Found: C, 67.10; H, 8.34; N, 3.30%. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CCl}_4}$ 1730 (s), 1530 (m, broad), 1370 (m), 1340 cm^{-1} (w); $\bigcup_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1540 (s), 1370 (m), 1340 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.34 (3H), 8.83 (3H), 8.28 (3H), 8.24 (3H), 8.06 (3H), 7.42 (1H, br. s.), 6.35 (3H), 5.36 (1H, d. of d., $J \approx 8$ and 2 c.p.s.), 4.15 (1H). Mass spectrum: m/e 400 (M-47, 8), 340 (13), 314 (100), 254 (10), 132 (43). Fractions 26-28 eluted with Skellysolve B-benzene (1:1, 50 ml) and benzene (100 ml) gave material (39 mg) which on crystallization from methanol afforded ketoacetate 376 (16 mg), m.p. 218-222°. Infrared spectrum: 1720 (s, broad), 1405 (w), 1370 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.14 (3m), 8.84 (3H), 7.98 (3H), 6.36 (3H), 5.34 (1H, br. d.). Mass spectrum: m/e 376 (molecular ion, 5), 316 (22), 290 (100), 257 (63), 121 (90). Fractions 29-31 eluted with benzene (250 ml) gave a yellow wax (91 mg) which crystallized on standing. Isolation of the pure nitroalcohol from this material by attempted recrystallization from a variety of solvents was not successful. It possessed the following spectral properties. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CHCl}_3}$ 3590 (m), 1720 (s), 1610 (m), 1500 (s), 1320 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.35 (3H), 8.58 (6H), 8.53 (3H), 6.28 (3H), 2.82 (1H). Ultraviolet spectrum: λ_{max} 362 m μ (5,560), 236 m μ (6250). Mass spectrum: m/e 403 (molecular ion, 20), 386 (29), 385 (26), 368 (33), 356 (18), 338 (27), 137 (50), 135 (74), 121 (27), 109 (46), 81 (48), 69 (19), 67 (26), 55 (49), 43 (100). Exact mass

measurement: m/e 403 (calc. for $C_{23}H_{33}NO_5$, 403.2359; found, 403.2373). Further elution of the column with benzene (300 ml) gave 31 mg of intractable material.

b) Structural Elucidation of the Deamination Products.

Acetate 402

i) Attempted pyrolysis of acetate 402

Acetate 402 (25 mg) was impregnated on glass beads in a glass tube and heated to 300° at 35 mm for one hour. A glassy solid condensed at the cool end of the tube and was found to be identical with the starting acetate 402.

ii) Conversion of acetate 402 (52) to ketone 54.

A solution of acetate 402 (24 mg) in anhydrous methanol (2.5 ml) containing sodium methoxide (5 mg) was allowed to stand at room temperature for 80 hours. The solution was then diluted with water (50 ml), acidified with concentrated hydrochloric acid and extracted with chloroform (2 x 30 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give alcohol 53 (22 mg) as a white foam. Infrared spectrum: $\nu_{\max}^{CCl_4}$ 3600 (m), 1720 (s), 1240 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.14 (3H), 8.84 (3H), 8.46 (3H), 8.37 (3H), 6.58 (1H, br. d.), 6.36 (3H). The mass spectrum showed a molecular ion at m/e 360.

To a solution of the above alcohol (22 mg) in acetone (4 ml), cooled to 10° , was added with stirring Jones' reagent (3 drops). After

five minutes the reaction mixture was treated with 5% potassium carbonate and then diluted with water. The product was extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give crude, oily ketone 54 (18 mg). A subdistilled sample possessed the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1725 (s), 1410 (w), 1245 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.06 (3H), 8.83 (3H), 8.44 (3H), 8.30 (3H), 6.37 (3H). The mass spectrum showed a molecular ion at m/e 358.

A solution of the above ketone in deuterated acetic acid containing deuterium chloride was allowed to stand at room temperature for 24 hours. The solvent was removed by codistillation with dry benzene under reduced pressure. The product obtained was intractable.

iii) Conversion of acetate 402 (52) to ketoolefin 56.

Ozone in oxygen was passed at a rate of 0.025 ml/sec for four minutes into a solution of acetate 402 (59 mg) in ethyl acetate (40 ml) cooled to -70° . The solution became blue. It was allowed to stand at -70° for two hours and then warmed to room temperature. The solvent was removed on the rotary evaporator and the residue heated with water (15 ml) and hydrogen peroxide (30%, 1.5 ml) on the steam bath for $1\frac{1}{2}$ hours. On cooling, the product was extracted with chloroform (2 x 30 ml). The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to afford a solid (56 mg).

This on recrystallization from methanol afforded ketoacetate 55a, m.p. , 217-222^o. Spectral comparison of this substance with ketoacetate 376 showed that the two are identical. The mass spectrum showed a molecular ion at m/e 376. Exact mass measurement revealed its composition as C₂₂H₃₂O₅ (calc. 376.2249; found 376.2247).

A solution of the above ketoacetate (25 mg) in aqueous methanol (1:3, 25 ml) containing potassium hydroxide (2.5 g) was refluxed for five hours. Most of the solvent was removed on the rotary evaporator. The residue was diluted with water (50 ml), acidified with concentrated hydrochloric acid and extracted with chloroform (3 x 50 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (20 mg). This material showed weak absorption due to a carboxyl group in the infrared. It was treated with ethereal diazomethane to obtain ketoalcohol 55b, m.p. 215-223^o. The infrared spectrum (CHCl₃) showed absorption at 3600 cm⁻¹.

In an earlier experiment dehydration of alcohol 55b was attempted with phosphorous oxychloride. A solution of ketoalcohol 55b (20 mg) in pyridine (3 ml), to which was added phosphorous oxychloride (0.6 ml), was allowed to stand at room temperature for 20 hours. The pyridine was removed by repeated codistillation with toluene on the rotary evaporator and the residue taken up in chloroform. The chloroform solution was washed with water, dried over anhydrous magnesium

sulfate and evaporated to afford a dark product (20 mg) which showed no absorption due to a hydroxyl group in the infrared. For purification chromatography on alumina was undertaken. The material was apparently destroyed on the column. Dehydration via cathylate was successful.

To an ice-cold solution of ketoalcohol 55b (22 mg) in pyridine (0.8 ml) was added dropwise freshly distilled ethyl chloroformate (0.6 ml). A red crystalline solid immediately precipitated. After one hour more ethyl chloroformate (0.3 ml) was added and the mixture was allowed to stand at room temperature overnight. The resulting brown colored solution was diluted with water (40 ml), acidified with concentrated hydrochloric acid and extracted with chloroform (2 x 25 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a greyish brown product (30 mg). This was dissolved in benzene and the solution filtered through alumina. Evaporation of the filtrate gave cathylate 55c (21 mg) as a white solid. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CCl}_4}$ 1750-1740 (s, broad), 1425 (w), 1370 (m), 1270 cm^{-1} (s).

The above cathylate was subjected to pyrolysis in a sealed tube at $240-250^\circ$ for $1\frac{1}{2}$ hours. The dark colored solid which resulted was sublimed at 140° under reduced pressure to afford greyish brown material (13 mg). This on resublimation at 95° under reduced pressure gave ketoolefin 56 (4 mg), m.p. $166-169^\circ$ (reported $166-168^\circ$).

Infrared spectrum: $\bigvee_{\text{max}}^{\text{CCl}_4}$ 1722 (s), 1612 (w), 1410 (w), 1250 cm^{-1} (s);

$\bigcup_{\text{max}}^{\text{KBr}}$ 1720 (s), 1610 (sh.), 1408 (w), 1252 cm^{-1} (m). A sample (10 mg) obtained from another experiment using 30 mg of ketoalcohol 55b was used to determine the n.m.r. spectrum. Nuclear magnetic resonance spectrum: τ 9.10 (3H), 8.85 (3H), 7.48 (1H, d., $J \approx 19$ c.p.s.), 6.35 (3H), 4.02-3.78 (2H, m, $J_{\text{AB}} \approx 8$ c.p.s.). Mass spectrum: m/e 316 (molecular ion, 1), 274 (100), 215 (10), 181 (44), 121 (62), 91 (39).
iv) Attempted conversion of acetate 402 to ~~to~~ acetate 76b.

A solution of acetate 402 (67 mg) in glacial acetic acid (3 ml) saturated with hydrogen chloride was allowed to stand at room temperature for 48 hours. The solvent was removed on the rotary evaporator and then under high vacuum. The brown colored product thus obtained possessed the following spectral characteristics. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CHCl}_3}$ 1725 (s), 1365 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.37, 8.97 (d; $J \approx 6.5$ c.p.s.), 8.86, 8.07, 6.36, 5.44 (broad), 4.69 attributable to acetate 76b constituting approximately one third of the mixture; other signals at τ 9.16, 8.98, 8.86, 8.84, 8.4, 8.0, 6.36, 5.7-5.22 (broad). Thin layer chromatography (silica gel) showed a single spot. The material was subjected to ozonolysis (ethyl acetate, -70°) and a product was obtained. Chromatography of this product on alumina gave ketoacetate 376 (8 mg). The remainder of the material was intractable.

Nitroacetate 400

i) Attempted hydrogenolysis.

A solution of nitroacetate 400 (18 mg) in methanol (30 ml) was

subjected to hydrogenation over Adams' catalyst (30 mg) at room temperature and 50 p.s.i. for 24 hours. The solution was filtered and the solvent evaporated to give 61 mg of product which contained large amounts of material from the rubber tubing. The product was dissolved in Skellysolve B and filtered through alumina to remove the extraneous material. Subsequent elution of the column with benzene-ether (9:1) gave 13 mg of material which crystallized from methanol and was found to be identical with the starting nitroacetate 400.

ii) Attempted pyrolysis.

Nitroacetate 400 (25 mg) was impregnated on glass beads in a glass tube and heated to $280-295^{\circ}$ at 35 mm for 2 hours. The oily material which condensed at the cool end of the tube was taken up in ether. Evaporation of the ether solution afforded a brownish yellow oil (7 mg). The infrared spectrum of the oil showed no absorption attributable to a nitro group. The ultraviolet spectrum showed absorption at $242\text{ m}\mu$. The n.m.r. spectrum showed three signals in the region τ 6.38-6.33. Further examination of the product was not undertaken.

Trinitro compound:

i) Attempted epoxidation.

To a solution of trinitro compound 60 (23 mg) in chloroform (10 ml) was added m-chloroperbenzoic acid (25 mg) and the solution was stirred for 3 hours. The solution was then shaken with dilute sodium sulfite

and neutralized with dilute sodium carbonate. The chloroform layer was separated, washed with water, dried over anhydrous magnesium sulfate and evaporated to give unchanged trinitro compound. Prolonged treatment (24 hours) of the trinitro compound with the peracid was also ineffective and gave unchanged starting material.

ii) Attempted ozonolysis of trinitro compound 60.

Ozone was passed at a rate of 0.025 ml/sec for 10 minutes into a solution of trinitro compound (19 mg) in chloroform (25 ml) at 0°. The solution was allowed to stand at 0° for one hour. Water (10 ml) was then added and the two-phase mixture heated on the steam bath for 2 hours. The chloroform layer was removed, dried over anhydrous magnesium sulfate and evaporated to give unchanged trinitro compound. In another experiment ozone was passed into the chloroform solution of trinitro compound for 3 hours. The trinitro compound was recovered unchanged.

iii) Transformation of trinitro compound 60 to dinitro compound 61.

A solution of trinitro compound 60 (180 mg) in chloroform (2 ml) was adsorbed on alumina (9 g). The top portion of the adsorbent immediately turned yellow. After 4 hours the column was eluted with chloroform (100 ml). Evaporation of the solvent gave a yellow foam (160 mg). A sample obtained by crystallization from ethanol was found to be identical in all respects with an authentic sample of dinitro compound 61.

Dinitro compound 61

i) Attempted reduction with Zn/HOAc.

To a solution of dinitro compound 60 (40 mg) in glacial acetic acid (3 ml) containing water (0.3 ml) was added, in small portions, zinc dust (150 mg). The mixture was heated on the steam bath. Shortly after the heating was started the yellow color of the reaction mixture vanished. After two hours the reaction mixture was filtered and the filtrate evaporated on the rotary evaporator. Water was added and the product extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a greyish foam (26 mg). The infrared spectrum (CCl_4) of this material showed absorption at 1730 (s), 1700 (sh.), 1620 (w), 1590 cm^{-1} (w). It was chromatographed over alumina. The material eluted from the column was intractable.

ii) Catalytic hydrogenation in ethanol.

A solution of dinitro compound 61 (43 mg) in ethanol (95%, 30 ml) was hydrogenated over Adams' catalyst (20 mg) at room temperature and atmospheric pressure. After an initial uptake of hydrogen (15 ml) in the first 15-20 minutes, no change in the burett reading was noticable. The hydrogenation was stopped after one hour, the solution filtered and evaporated to give a white foam (40 mg). This material showed absorption at 3580 (m), 1720 (s), 1545 (m), 1350 cm^{-1} (m) in the infrared spectrum (CHCl_3). It was acetylated with acetic anhydride

in pyridine to afford brown colored material (45 mg) which showed absorption at 1760 (s), 1720 (s), 1670 (m), 1545 (s), 1370 (m), 1350 cm^{-1} (m) in the infrared spectrum (CHCl_3). The acetylated material was subjected to chromatography on neutral alumina (3 g, Woelm grade II). Early fractions eluted with benzene (60 ml) gave material (14 mg) which crystallized from methanol to afford colorless needles of N-acetate I (6 mg), m.p. 80-81^o. (For physical properties see the section on catalytic hydrogenation in ethanol-HCl). Elution with benzene-ether (9:1) gave material (5 mg) which showed absorption at 3440 (sharp), 1670 (s), 1540 cm^{-1} (s). Further elution with more polar solvents gave intractable material.

iii) Catalytic hydrogenation in ethyl acetate.

A solution of dinitro compound 61 (100 mg) in ethyl acetate (30 ml) was hydrogenated over Adams' catalyst (33 mg) at room temperature and atmospheric pressure. After an initial absorption of hydrogen (24.4 ml) in the first 30 minutes, no change in the burette reading was noticable. The hydrogenation was stopped after one hour. The solution was filtered and evaporated to afford a white foam (95 mg) which showed absorption at 3580 (m), 1720 (s), 1540 (s), 1350 cm^{-1} (m) in the infrared spectrum (CHCl_3). The material was dissolved in ether and the solution extracted with dilute hydrochloric acid. Basic (12 mg) and nonbasic (72 mg) fractions were thus obtained. The basic fraction on acetylation ($\text{Ac}_2\text{O}/\text{Py}$) gave the acetylated product which

crystallized from methanol to afford N-acetate I (5 mg). The nonbasic fraction was similarly acetylated to give a product which showed absorption at 1760 (s), 1720 (s), 1620 (w), 1540 (s), 1370 (m), 1350 cm^{-1} (m) in the infrared. This product was subjected to chromatography on silica gel (6 g). Fractions eluted with benzene (125 ml) gave material (17 mg) which crystallized from ethanol to afford colorless needles of compound 62 (10 mg) m.p. 136-138°. Extensive recrystallization from ethanol furnished a pure sample, m.p. 140-140.5°. Calc. for $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_6$: C, 63.57; H, 7.89; N, 6.45%. Found: C, 63.46; H, 7.73; N, 6.36%. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1605 (w), 1540 (v.s.), 1350 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 8.95 (3H), 8.69 and 8.63 (3H, 3:1), 8.35 and 8.31 (6H, 1:3), 6.39 (1H, m), 6.35 and 6.33 (3H, 3:1), 5.28 (1H, m.), 4.69 and 4.45 (1H, 3:1). Simultaneous irradiation 361 c.p.s. downfield from TMS caused sharpening of the signals at τ 4.69 and τ 4.45 and a simplification of the multiplet at τ 5.28. Mass spectrum: m/e 388 (M-46, 8); 358 (28), 341 (100), 281 (54), 121 (44), 107 (69), 105 (52), 91 (57). Exact mass measurement: m/e 388 (calc. for $\text{C}_{23}\text{H}_{34}\text{NO}_4$, 388.2488; found, 388.2489), 358 (calc. for $\text{C}_{23}\text{H}_{34}\text{O}_3$, 358.2508; found, 358.2505), 341 (calc. for $\text{C}_{23}\text{H}_{33}\text{O}_2$, 341.2481; found, 341.2478), 281 (calc. for $\text{C}_{21}\text{H}_{29}$, 281.2269; found, 281.2267). Further elution with more polar solvents gave intractable material.

In an earlier experiment the hydrogenation product was acetylated

without separating basic and nonbasic fractions. Chromatography of the acetylated product on silica gel afforded compound 62. The remainder of the material on rechromatography over alumina gave a small amount of N-acetate I.

iv) Catalytic hydrogenation in ethanol-HCl.

A solution of dinitro compound 61 (170 mg) in ethanol (40 ml) containing a few drops of concentrated hydrochloric acid was hydrogenated over Adams' catalyst (60 mg) at room temperature and atmospheric pressure. Most of the hydrogen absorption (80.8 ml) occurred during the first hour with only a small volume (1.2 ml) being absorbed in the next 6 hours. After 7 hours the hydrogenation was stopped. The solution was filtered and evaporated on the rotary evaporator. The residue was dissolved in ether and transferred to a separatory funnel. The small ether insoluble portion was dissolved in water and also transferred to the separatory funnel. The ether solution was extracted with dilute hydrochloric acid (1N, 2 x 30 ml), washed with water (2 x 30 ml) dried and evaporated to give the non-basic product (24 mg). The acidic extract and the washings were combined, basified with sodium carbonate, and extracted with ether. The ether solution, after being dried over anhydrous magnesium sulfate was evaporated to give the basic product (118 mg). This was acetylated with acetic anhydride in pyridine. The acetylated material on crystallization from methanol gave N-acetate I (70 mg). Recrystallization from methanol afforded

the analytical sample, m.p. 80-81°. Calc. for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47%. Found: C, 74.57; H, 10.24; N, 3.49%.

Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3370 (m, broad), 1715 (s), 1660 (s), 1540 (s), 1375 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.15 (3H, d., $J \approx 6$ c.p.s.), 9.14 (3H, d., $J \approx 6$ c.p.s.), 8.87 (3H), 8.75 (3H), 8.00 (3H), 6.33 (4H), 3.0 (1H, broad s.). In deuterated pyridine: τ 9.18 (3H, d., $J \approx 6$ c.p.s.), 9.16 (3H, d., $J \approx 6$ c.p.s.), 8.94 (3H), 8.72 (3H), 7.84 (3H), 6.32 (3H), 6.08 (1H, br. s.), 2.57 (1H, br. s.). The signal at τ 6.08 sharpened on simultaneous irradiation 743 c.p.s. downfield from TMS. Mass spectrum: m/e 403 (molecular ion, 22), 344 (100), 329 (67), 301 (58), 285 (95), 284 (78), 273 (48), 269 (50), 241 (30), 213 (21), 133 (32), 109 (42), 107 (32), 105 (43). Exact mass measurements: m/e 403 (calc. for $C_{25}H_{41}NO_3$, 403.3086; found, 403.3081), 344 (calc. for $C_{23}H_{36}O_2$, 344.2712; found, 344.2715). The noncrystalline acetylated material (50 mg) was chromatographed on alumina (4 g). Elution with benzene (80 ml) gave an unidentified oil (3 mg). Elution with benzene-ether (19:1, 120 ml) and benzene-ether (9:1, 40 ml) gave N-acetate I (13 mg). Continued elution with benzene-ether (9:1, 80 ml) gave unidentified material (2 mg). Further elution with the same solvent (200 ml) gave material (17 mg) which contained N-acetate II as the major component. This material possessed the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3440 (sharp), 3360 (broad), 1725 (s), 1670 (s), 1540 (m), 1520 (s),

1350 cm^{-1} (m) (underlined absorptions attributable to the minor component).

Nuclear magnetic resonance spectrum: τ 9.13 (3H, d., $J \approx 6$ c.p.s.), 9.11 (3H, d., $J \approx 6$ c.p.s.), 8.88 (3H), 8.78, 8.72 (3H), 9.06 (3H), 7.97, 6.30, 6.26 (3H), 6.10 (broad signal), 4.66 (broad signal) (the underlined signals attributable to the minor component). Mass spectrum: m/e 403 (molecular ion); the fragmentation pattern was essentially the same as that of N-acetate I. Elution with chloroform (40 ml) gave material (12 mg) which spontaneously crystallized during evaporation of the solvent. A sample washed with ether melted at 235-236° (decomposition). Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3435 (sharp), 1725 (s), 1675 (s), 1540 (s), 1500 (s), 1350 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.27 (3H), 8.83 (3H), 8.25 (3H), 8.21 (3H), 7.91 (3H), 6.35 (3H), 5.95 (1H, br. d.), 5.37 (1m, broad). Mass spectrum: m/e 482 (2.4) 480 (5.4), 398 (100), 374 (52), 38 (3.4), 36 (11). Exact mass measurement: m/e 480 (calc. for $\text{C}_{25}\text{H}_{37}\text{N}_2\text{O}_5^{35}\text{Cl}$: 480.2392; found 480.2395), 374 (calc. for $\text{C}_{23}\text{H}_{31}\text{O}_2^{35}\text{Cl}$: 374.2013; found: 374.2017).

v) Preparation and isolation of the sulfonamides 66-68.

A solution of dinitro compound 61 (330 mg) in ethanol containing hydrochloric acid was hydrogenated and the basic product (198 mg) was obtained by the procedure described above. To a solution of the basic product in dry pyridine (80 drops) was added methanesulfonyl chloride (16 drops) and the resulting solution was allowed to stand at room

temperature for 3 hours. Dilute hydrochloric acid (1N, 40 ml) was then added and the product extracted with ether (100 ml). The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a mixture of sulfonamides (227 mg). Crystallization of this material from methanol afforded colorless plates (106 mg) of sulfonamide I (66), m.p. 177°. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 33225 (m, broad), 1705 (s), 1330 (s), 1150 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.16 (3H, d., $J \approx 6$ c.p.s.), 9.13 (3H, d., $J \approx 6$ c.p.s.), 8.88 (3H), 8.75 (3H), 7.12 (3H), 6.70 (1H, br. s.), 6.32 (3H), 3.87 (1H, br. d., $J \approx 6$ c.p.s.). The signal at τ 6.7 became sharper on simultaneous irradiation 613 c.p.s. down-field from TMS. Mass spectrum: m/e 439 (molecular ion, 55), 360 (66), 344 (100), 329 (39), 301 (24), 285 (68), 284 (56), 217 (93), 105 (50), 81 (58), 79 (54). Exact mass measurement: m/e 439 (calc. for $\text{C}_{24}\text{H}_{41}\text{NO}_4^{32}\text{S}$: 439.2757; found: 439.2752). The noncrystalline residue (147 mg, from two experiments) was subjected to chromatography on alumina (9 g). Fractions eluted with benzene (90 ml), benzene-ether (9:1, 180 ml) and benzene-ether (85:15, 180 ml) gave material (30 mg) which on crystallization from methanol afforded sulfonamide I (14 mg). Elution with benzene-ether (1:1, 60 ml) and ether (180 ml) gave material (14 mg) which crystallized spontaneously during evaporation of the solvent. A sample crystallized from methanol afforded colorless needles of sulfonamide II, m.p. 206-209°. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$

3380 (m, sharp), 1720 (s), 1330 (s), 1150 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.11 (3H, d., $J \approx 6$ c.p.s.), 9.10 (3H, d., $J \approx 6$ c.p.s.), 8.89 (3H), 8.78 (3H), 7.09 (3H), 6.54 (1H; broad singlet), 6.34 (3H), 5.66 (1H, d., $J \approx 7.5$ c.p.s.). The doublet at τ 5.66 collapsed to a singlet on simultaneous irradiation 346 c.p.s. downfield from TMS. Mass spectrum: m/e 439 (molecular ion, calc. for $\text{C}_{24}\text{H}_{41}\text{NO}_4^{32}\text{S}$: 439.2757; found, 439.2752). The fragmentation pattern was similar to that of sulfonamide I.

Elution with chloroform (60 ml) gave material (50 mg) which appeared to be mainly chloro-sulfonamide 68. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3360 (m, sharp), 1725 (s), 1545 (s), 1340 (s), 1140 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.30 (3H), 8.82 (3H), 8.26 (3H), 8.22 (3H), 6.90 (3H), 6.29 (3H), 5.97 (1H, br. d., $J \approx 10$ c.p.s.), 5.72 (1H, d. of d., $J \approx 8.5$ and 3 c.p.s.), 5.07 (1H, d., $J \approx 10$ c.p.s.), 4.15 (1H, br. s.). Purification of this material by chromatography on alumina gave a product which crystallized from Skellysolve B-ether to afford colorless plates of the chlorosulfonamide 68, m.p. 188-191 $^{\circ}$ (decomposition). Mass spectrum: m/e 472 (M-46, 22), 470 (M-46, 54), 377 (32), 375 (96), 315 (58), 313 (43), 312 (56), 144 (100), 107 (72), 38 (2), 36 (7). Exact mass measurement: m/e 470 (calc. for $\text{C}_{24}\text{H}_{37}\text{NO}_4^{32}\text{S}^{35}\text{Cl}$: 470.2129; found, 470.2129).

vi) Attempted pyrolysis of the N-nitroso derivative of N-acetate I (63).

A solution of N-acetate I (65 mg) in glacial acetic acid (5 ml)

containing fused sodium acetate (0.5 g) was added with stirring to a solution of dinitrogen tetroxide (≈ 0.25 g) in 0.7 ml of the same solvent. After 5 hours of stirring at room temperature the solution was diluted with ether (80 ml) and washed with water (3 x 30 ml). The ether solution was dried over anhydrous magnesium sulfate and evaporated to give a brown colored foam (58 mg) which showed absorption at 1730 (s), 1665 (m), 1545 (s, broad), 1375 cm^{-1} (m) in the infrared. This material on crystallization from methanol gave unchanged N-acetate I (10 mg). The noncrystalline residue was chromatographed on alumina. This gave a further small amount of N-acetate I (7 mg). The remainder of the eluted material was intractable.

vii) Attempted reductive deamination.

A suspension of sulfonamide I (170 mg) in 12% sodium hydroxide (20 ml) and ethanol (10 ml) was heated on the steam bath. On heating a clear solution resulted. Hydroxylaminesulfonic acid (1.02 g) was added to the solution over a period of 30 minutes and heating on the steam bath was resumed. After 22 hours the reaction mixture was diluted with water (25 ml), acidified with concentrated hydrochloric acid and extracted with ether (125 ml). The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (166 mg). The infrared spectrum of this material showed weak absorption attributable to a carboxyl group. On treatment with ethereal diazomethane the material crystallized and was found to be

identical with the starting sulfonamide. Use of sodium methoxide-methanol and potassium tert-butoxide-tertiary butanol in the reaction was also unsuccessful and unchanged sulfonamide I was recovered.

Nitroalcohol 73

i) Conversion of nitroalcohol 73 to N-acetate I (63).

A solution of nitroalcohol rich material (40 mg) in ethanol acidified with concentrated hydrochloric acid was hydrogenated over Adams' catalyst. The hydrogenation product on work-up gave basic (9 mg) and nonbasic (21 mg) fractions. The basic material was acetylated with acetic anhydride and pyridine. The product obtained gave on crystallization from methanol a crystalline substance (3 mg) which was found to be identical with N-acetate I by infrared and t.l.c. comparison.

ii) Attempted dehydration of nitroalcohol with thionyl chloride.

A solution of nitroalcohol (80 mg) in methylene chloride (10 ml) containing thionyl chloride (1 ml) was allowed to stand at room temperature for 18 hours. Excess thionyl chloride was removed by repeated codistillation with benzene on the rotary evaporator, and traces of the solvent were removed on the vacuum pump. This gave a yellow foam which possessed the following spectral properties. Infrared spectrum:

$\bigcup_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1610 (m), 1500 (m), 1320 cm^{-1} (s), no absorption in the hydroxyl region. Nuclear magnetic resonance spectrum: τ 9.33 (3H) 8.51 (3H), 8.23 (3H), 8.17 (3H), 6.29 (3H), 2.87 (1H). Ultraviolet

spectrum: λ_{\max} 357 m μ , 237 m μ . The product was hydrogenated in ethanol (30 ml) over Adams' catalyst (21 mg) at room temperature and atmospheric pressure. After two hours the solution was filtered and evaporated to give a yellowish material (71 mg). This was acetylated with acetic anhydride in pyridine and the product chromatographed on alumina (5 g). Elution with benzene (150 ml) gave an unidentified oily material (16 mg). Elution with benzene-ether (19:1, 100 ml) and benzene-ether (85:15, 50 ml) gave material (15 mg) which crystallized from methanol to afford a crystalline compound (7 mg). A recrystallized sample, m.p. 80-81^o was found to be identical in all respects with N-acetate I (63). Further elution with more polar solvents gave intractable material.

For the purposes of determining the mass spectrum and obtaining elemental analysis another experiment involving the reaction of thionyl chloride with nitroalcohol 73 was carried out. The mass spectrum of the product showed the ion of highest mass at m/e 386 (v. weak). Other important peaks: m/e 385 (1), 119 (100), 38 (32), 36 (93). Elemental analysis, calc. for C₂₃H₃₂NO₄Cl: Cl, 8.42%. Found: Cl, 7.90, 8.47%.

iii) Acid catalysed dehydration of nitroalcohol 73.

A solution of nitroalcohol 73 (25 mg) in dry benzene (25 ml) containing p-toluenesulfonic acid (2.5 mg) was refluxed on the steam bath for one hour. The solution was allowed to cool and then diluted

with ether (40 ml). The benzene-ether solution was washed with 5% sodium carbonate (25 ml) followed by water (2 x 20 ml). It was then dried over anhydrous magnesium sulfate and evaporated to give nitrotriene 75 as a yellow wax (24 mg). Infrared spectrum: $\nearrow_{\text{max}}^{\text{CHCl}_3}$ 1730 (s), 1620 (w), 1600 (w), 1500 (m), 1320 (s), 900 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.34 (3H), 8.50 (3H), 8.00 (3H), 6.29 (3H), 4.80 (1H), 4.59 (1H), 2.77 (1H). Ultraviolet spectrum: λ_{max} 382 $\text{m}\mu$ (5450), 258 (6270). Mass spectrum: m/e 385 (molecular ion, 2.4), 368 (1.5), 223 (36), 57 (100).

Attempted crystallization of nitrotriene 75 from hot ethanol led to the decomposition and formation of intractable product.

3. THE SOLVOLYTIC APPROACH

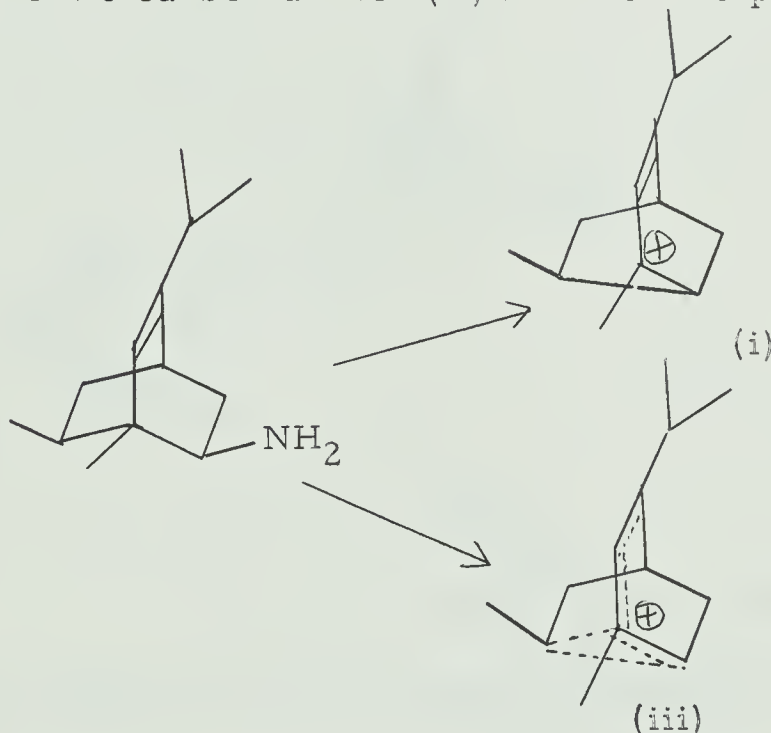
The approach to the construction of a bicyclo[3.2.1]octane system from a bicyclo[2.2.2]octane system, involving deamination of amine 29 (R = CH₃) was not completely satisfactory. To sum up the unsatisfactory aspects of this approach:

- a) Nitrous acid deamination of amine 29 furnishes a mixture containing a large number of compounds. They are comprised of alcohols, acetates and nitrated substances and their isolation is tedious.
- b) Compounds having the unrearranged bicyclo[2.2.2]octane system form a substantial portion of the deamination product.
- c) Compounds having the rearranged skeleton with a bicyclo[3.2.1]octane system generally appear to be nitrated.

The nitro groups present difficulties in their replacement by or transformation to suitable functions that might be of potential use in further synthetic schemes.

Clearly, there was a need to develop an alternative method for effecting the desired rearrangement. Two factors appear to be mainly responsible for making the deamination reaction complicated. One is the presence of the \triangle^{7-8} double bond in amine 29 and the other is the generation of oxides of nitrogen from nitrous acid in the reaction mixture. A detailed consideration of their involvement in the side reactions will be found in the last chapter of this thesis.

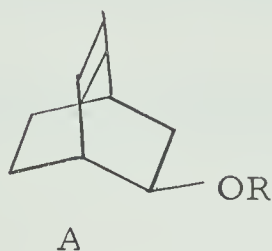
One possible way to alleviate the situation appeared to be deamination of a saturated analog obtained by catalytic hydrogenation of amine 29. It should be borne in mind that although hydrogenation of the \triangle^{7-8} double bond in amine 29 might be advantageous in so far as its possible involvement in a reaction with oxides of nitrogen is concerned it is likely to affect adversely the efficiency of the rearrangement. This is easy to see if one considers the additional stability imparted by the \triangle^{7-8} double bond to the carbonium ion (i) in an allylic position or alternatively to the carbonium ion (ii) in which the positive charge is



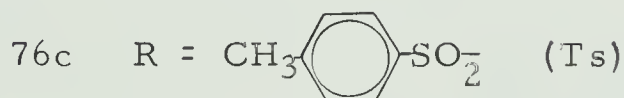
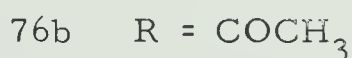
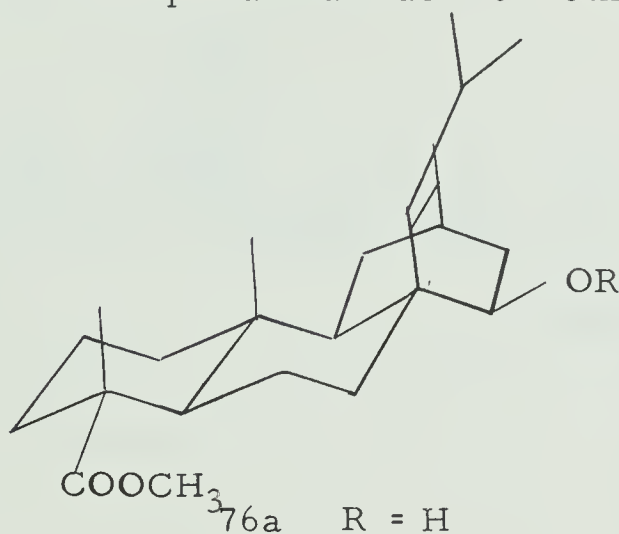
delocalized over five centres. Deamination of the saturated amine could not however be undertaken since attempts to hydrogenate the \triangle^{7-8} double bond in amine 29 were unsuccessful.

Another approach to the problem involved abandoning the nitrous acid deamination in favor of a method that was less likely to involve complicated side reactions. As mentioned in the introductory section

the rearrangement of a bicyclo[2.2.2]octene system to a bicyclo[3.2.1]octene system has been brought about^{21b} by acetolysis of the model compound A (R = Ts).



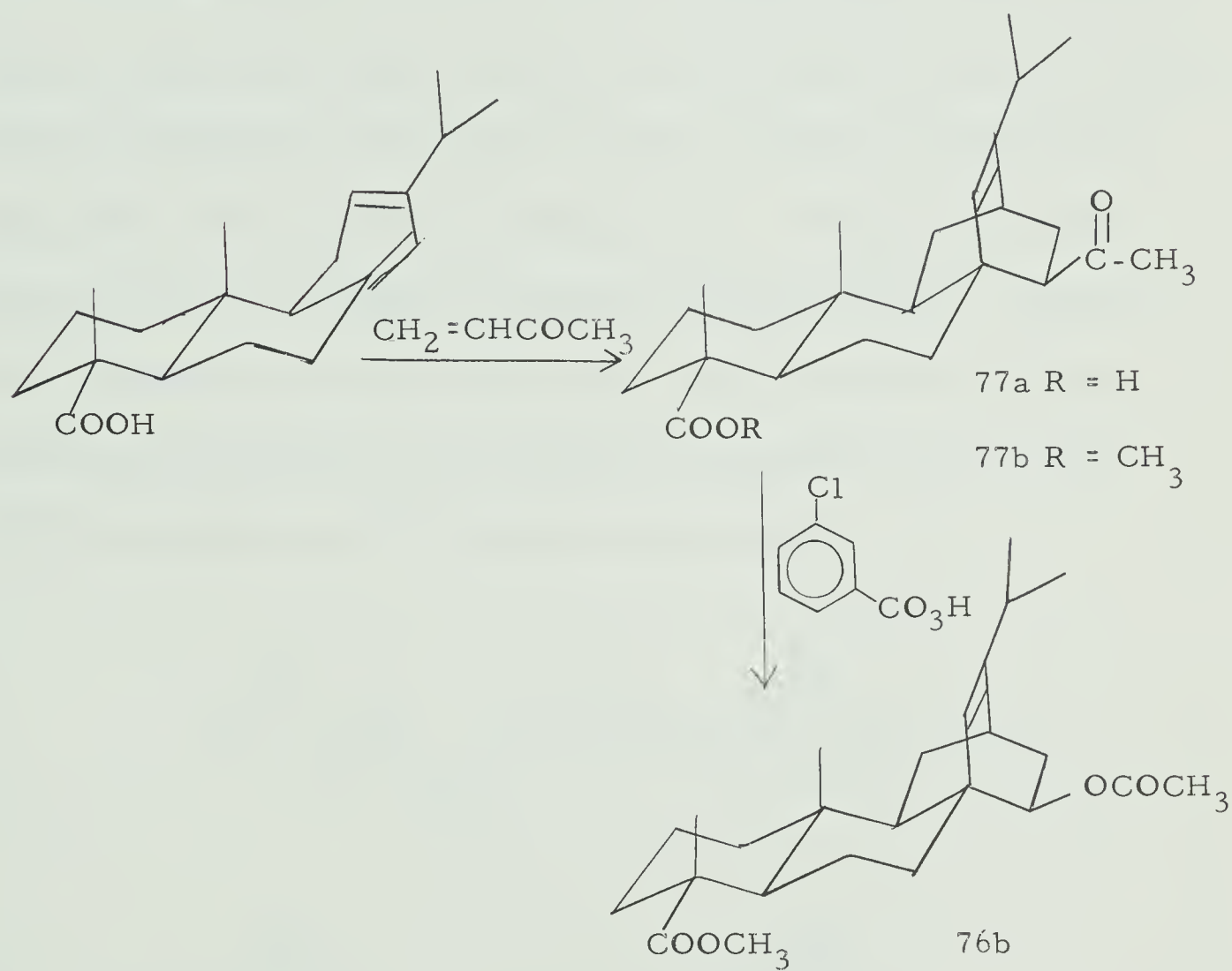
The first objective in this approach was the synthesis of the tosylate 76c. A simple and attractive method for the synthesis of this



compound was suggested by the method of synthesis of the model compound A which was obtained by the Diels-Alder reaction between cyclohexadiene and vinyl acetate. The reaction between methyl levopimarate and vinyl acetate would be expected to give the adduct 76b which could then be transformed into the tosylate 76c via the alcohol 76a. This simple scheme for the preparation of tosylate 76c, however, was not undertaken since an attempted reaction between abietic acid

(in equilibrium with levopimaric acid at high temperatures) and vinyl acetate is reported to have failed⁶¹. Synthesis of acetate 76b by an alternative route (Scheme 1) was therefore undertaken.

Attempted Synthesis of 76b from the Levopimaric Acid-Methyl Vinyl
Ketone Adduct.

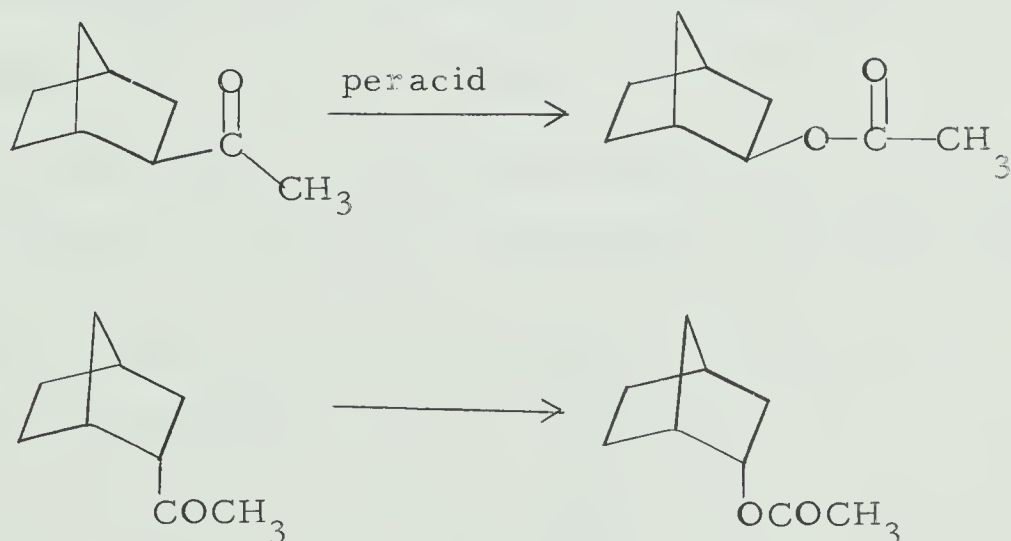


Scheme 1

This scheme involves a Diels-Alder reaction between levopimaric acid and methyl vinyl ketone to obtain the adduct 77a as the first step. The formation of 77a as the predominant product in this reaction was expected by analogy with the formation of adduct 31. It

was expected that the conversion of 77a or the corresponding methyl ester 77b to the acetate 76b could be carried out by means of the Baeyer-Villiger reaction. The following considerations led us to believe that the acetyl compound 77b might give the desired acetate 76b by this reaction.

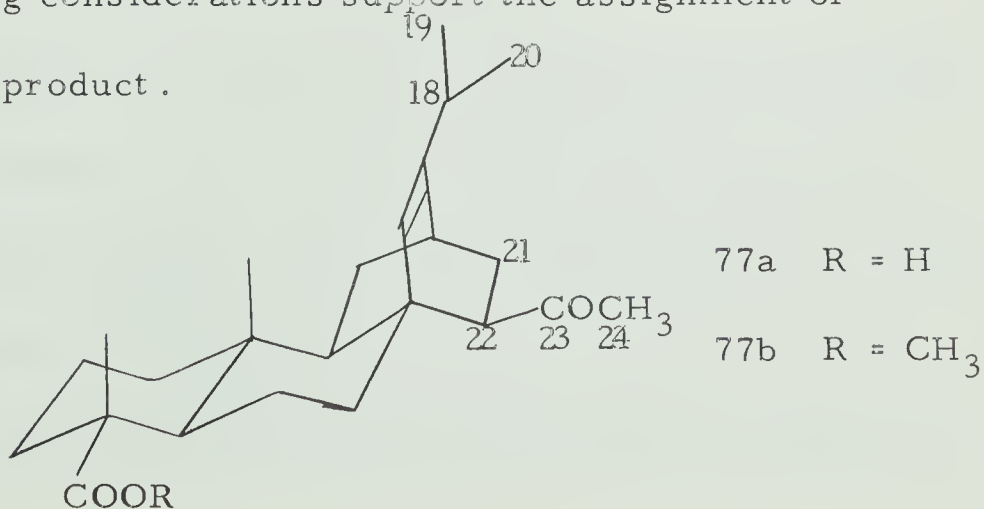
It is an observed fact that methyl alkyl ketones, when treated with peracids, form alkyl acetates as the predominant products. This has been explained on the basis of a higher migratory aptitude of the alkyl group with respect to the methyl group. Bridged ring methyl ketones also form acetates in a Baeyer-Villiger reaction. Furthermore the stereochemistry at the carbon atom bearing the acetoxy group is retained during rearrangement. An example of a bicyclo [2.2.1] heptyl derivative⁶² illustrates these points.



Ordinarily a double bond is more reactive (to form epoxides) than a ketone toward peracids. The \triangle^{7-8} double bond in the acetyl compound 77b however, was expected to be highly hindered as is the

case with the amine 29 and methyl maleopimarate. Attempts to hydrogenate the \triangle^{7-8} double bond in amine 29 had not been successful. Zalkow^{63a} has reported failure of m-chloroperbenzoic acid to effect the epoxidation of the double bond in methyl maleopimarate but more powerful reagents like m-nitroperbenzoic acid^{63a} and trifluoroperacetic acid^{63b}, have been used successfully. In view of this it was felt that the acetyl compound 77b, on treatment with m-chloroperbenzoic acid might furnish the desired acetate 76b as the predominant product. Accordingly synthesis of 76b by Scheme 1 was undertaken.

Preparation of the acetyl compound 77a posed no problem. A benzene solution of levopimaric acid containing an excess of methyl vinyl ketone and a few crystals of hydroquinone was refluxed for 8 hours. The product, obtained after removal of unreacted methyl vinyl ketone and the solvent, was treated with cyclohexylamine to give a crystalline salt. On decomposition with dilute phosphoric acid this salt gave crude adduct 77a which was crystallized from acetonitrile to afford a crystalline product (m.p. 135-136°) in ca. 55% overall yield. The following considerations support the assignment of structure 77a to the product.



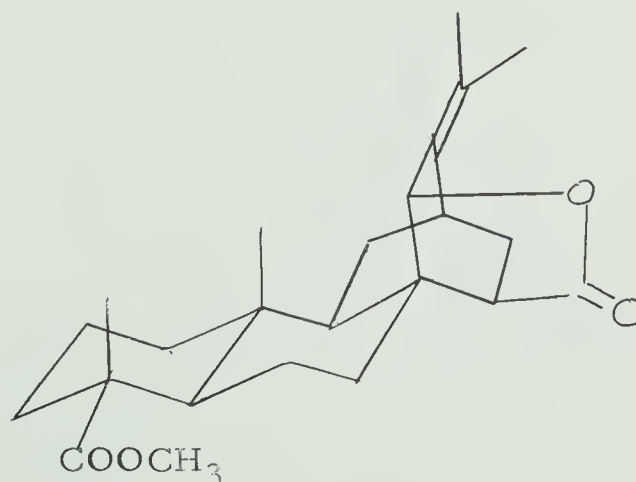
The presence of a carboxylic group in 77a was indicated by the infrared spectrum which shows absorption at 1700 cm^{-1} (s) and $2400\text{--}3200\text{ cm}^{-1}$ (br.). Presumably the carbonyl stretching absorption of the C-22 acetyl function overlaps the band at 1700 cm^{-1} due to the C-1 carboxyl. The presence of the C-22 acetyl group is apparent from the three proton singlet at $\tau 8.07$ in the n.m.r. spectrum of compound 77a. The somewhat high chemical shift of the C-22 acetyl is suggestive of its endo orientation in which the protons on C-24 are shielded by the \triangle^{7-8} double bond. In agreement with structure 77a the C-12 methyl (shielded by the \triangle^{7-8} double bond) gives rise to a three proton singlet at $\tau 9.38$ and the C-1 methyl appears at $\tau 8.86$. The six proton doublet ($J = 6.5\text{ c.p.s.}$) at $\tau 8.95$ can be readily assigned to the C-18 methyl groups. The presence of a trisubstituted double bond and a carboxyl group is indicated by the signals at $\tau 4.58$ and $\tau -0.75$ (br) respectively.

Further support for the assigned structure 77a comes from the properties shown by the methyl ester 77b which was obtained by treatment of adduct 77a with ethereal diazomethane.

The mass spectrum of compound 77b gave a molecular ion at $m/e\ 386$ which is consistent with the molecular formula $\text{C}_{25}\text{H}_{38}\text{O}_3$. The base peak occurs at $m/e\ 43$. This can be explained on the basis of an α cleavage of the C-22 acetyl side chain to produce the ion $\begin{array}{c} \text{O}^+ \\ || \\ \text{C}-\text{CH}_3 \end{array}$, $m/e\ 43$. The infrared spectrum of 77b shows two bands in

the carbonyl region. The absorption at 1700 cm^{-1} is attributed to the ketone and that at 1730 cm^{-1} is assigned to the C-1 carbomethoxy group. The presence of the latter is also indicated in the n.m.r. spectrum which shows a signal at $\tau 6.36$ (3H, s). The other n.m.r. data for the methyl ester are consistent with the formulation 77b.

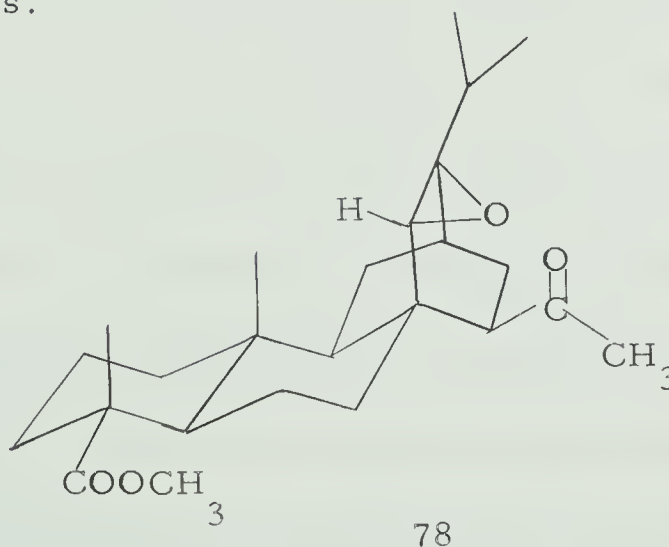
In order to confirm that the acetyl group in 77a is attached to C-22, and is endo oriented the compound was subjected to oxidation with sodium hypobromite. The aim was to obtain the lactonic product which would result by oxidation of C-22 acetyl to C-22 carboxyl followed by bromolactonization. Following the procedure of Levine⁶⁴ et al compound 77a was treated with an alkaline solution of bromine. The product obtained was first esterified with ethereal diazomethane and then subjected to chromatography on neutral alumina. A crystalline substance was isolated ($\approx 11\%$) from the middle fractions eluted with benzene. Comparison of this crystalline substance with an authentic sample of the isopropylidene lactone 39 established that the two were identical. Since the formation of isopropylidene lactone is possible



only if the acetyl group is located on C-22 and is endo oriented the structure assigned to compound 77a is confirmed.

The chromatography on neutral alumina gave another crystalline compound ($\approx 7\%$) which also appears to be a lactone (IR). The exact nature of this compound was not determined.

With the ketone 77a of the desired structure in hand, attention was turned to the next step involving a Baeyer-Villiger reaction. A benzene solution of the methyl ester 77b (obtained from 77a by treatment with ethereal diazomethane) was treated with an excess (1.5 equiv.) of m-chloroperbenzoic acid. The progress of the reaction was monitored by determining the infrared spectra (observation of the ketone band at 1700 cm^{-1}) of aliquots withdrawn at regular intervals. The decrease in the intensity of the band at 1700 cm^{-1} was slow but several new bands began to appear. After a period of twelve days the reaction was stopped and a product, which appeared to be mainly one compound, was isolated. Structure 78 is proposed for this compound on the basis of its spectral properties.

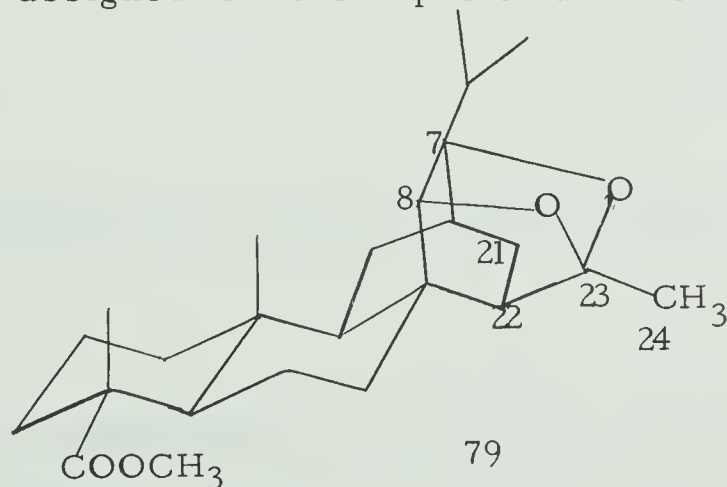


The presence of a methyl ketone is deduced from the band at 1700 cm^{-1} in the infrared and the three proton signal at $\tau 7.98$ in the n.m.r. spectrum. Consistent with the oxirane ring formation at C 7-8 the n.m.r. spectrum of compound 78 shows a signal at $\tau 6.90$ (1H, s) attributable to the proton on C-8 and a signal at $\tau 9.19$ (3H, s) assignable to the C-12 methyl group which is no longer shielded by a double bond. The C-18 methyls appear as a pair of doublets ($J = 7.5$ c.p.s.) at $\tau 9.28$, and $\tau 8.94$. The nonequivalence of these methyls is not unexpected since the isopropyl group on C-7 is in an asymmetric environment⁵⁴. The C-1 methyl and the C-1 carbomethoxyl give rise to the signals at $\tau 8.85$ and $\tau 6.37$ respectively. The presence of the C-1 carbomethoxyl is also indicated in the infrared spectrum by a band at 1730 cm^{-1} . The n.m.r. spectral data for compound 78 are comparable to those reported by Langlois *et al*^{63b} for the C-7, C-8 oxide of methyl maleopimarate.

Formation of the epoxide 78 in a Baeyer-Villiger reaction made it clear that the conversion of the C-22 acetyl group to a C-22 acetoxy group was not possible with m-chloroperbenzoic acid. Monoperphthalic acid was also ineffective in bringing about the desired conversion. Before closing dicussion on the synthesis of compound 76b an interesting transformation of the epoxide 78 to the ketal 79 will be described.

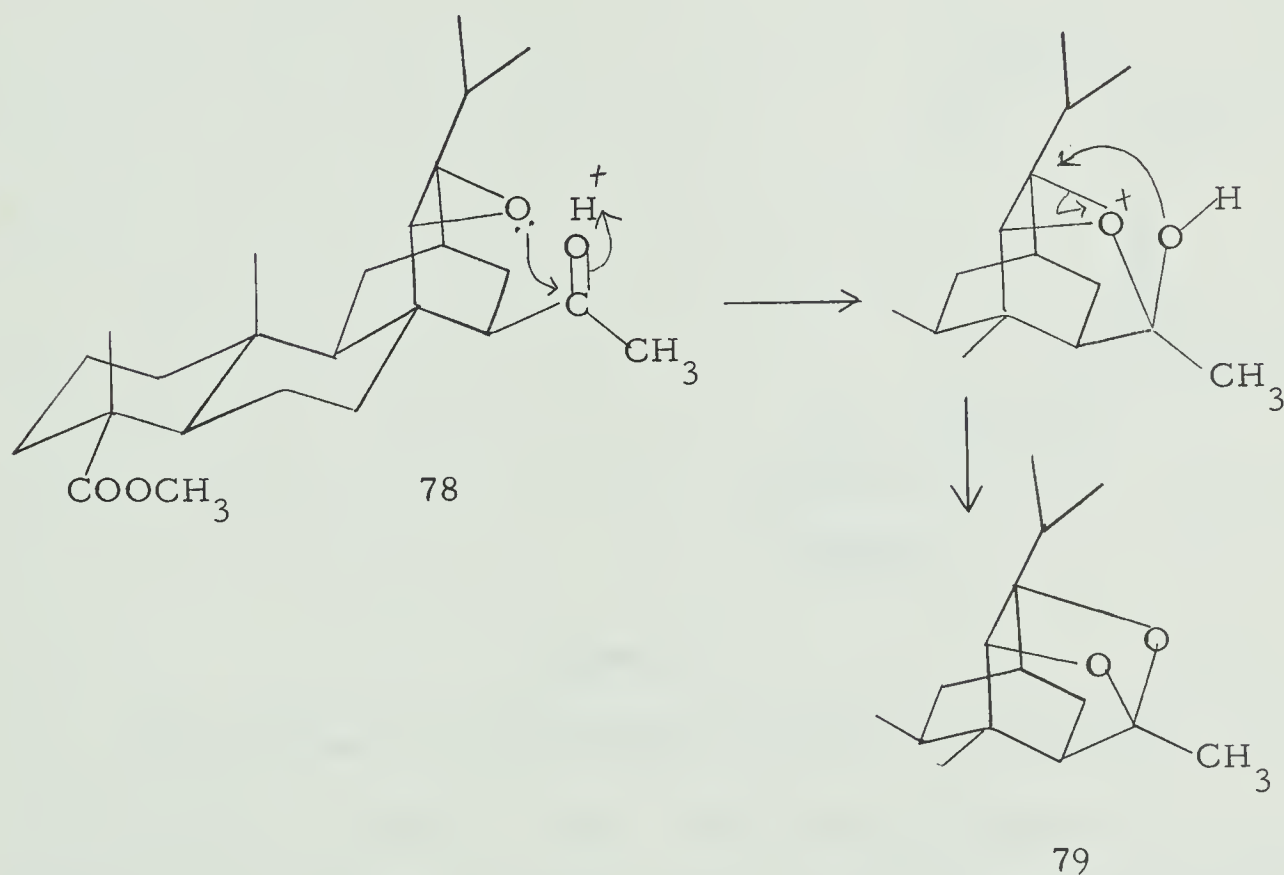
The epoxide 78 was isolated from the attempted Baeyer-Villiger reaction as a white foam and could not be induced to crystallize. How-

ever after standing for a few days (in the presence of traces of CHCl_3) the foam spontaneously crystallized. Surprisingly the spectral properties of the crystalline substance (m.p. $149-150^\circ$) were different from those of the epoxide 78. The mass spectrum of the new compound gave a molecular ion at m/e 402 indicating that its molecular composition is the same as that of epoxide 78. The infrared spectrum of the crystalline substance shows a single band in the carbonyl region at 1715 cm^{-1} attributable to the C-1 carbomethoxy group, the presence of which is also indicated by a signal at τ 6.37 (3H, s) in the n.m.r. spectrum. The absence of an acetyl group as indicated by the infrared was confirmed by the n.m.r. spectrum which does not show any signal attributable to an acetyl group. The signals at τ 8.84 (3H, s), τ 9.04 (3H, s) and τ 9.06 (6H, d, $J = 7\text{ c.p.s.}$) can be assigned to the C-1, the C-12 and the C-18 methyls respectively. Two other signals in the n.m.r. spectrum of the crystalline substance remain unaccounted for. One of these appears at τ 5.73 (1H, s) and the other at τ 8.50 (3H, s). The former can be assigned to the C-8 proton and the latter to the C-23



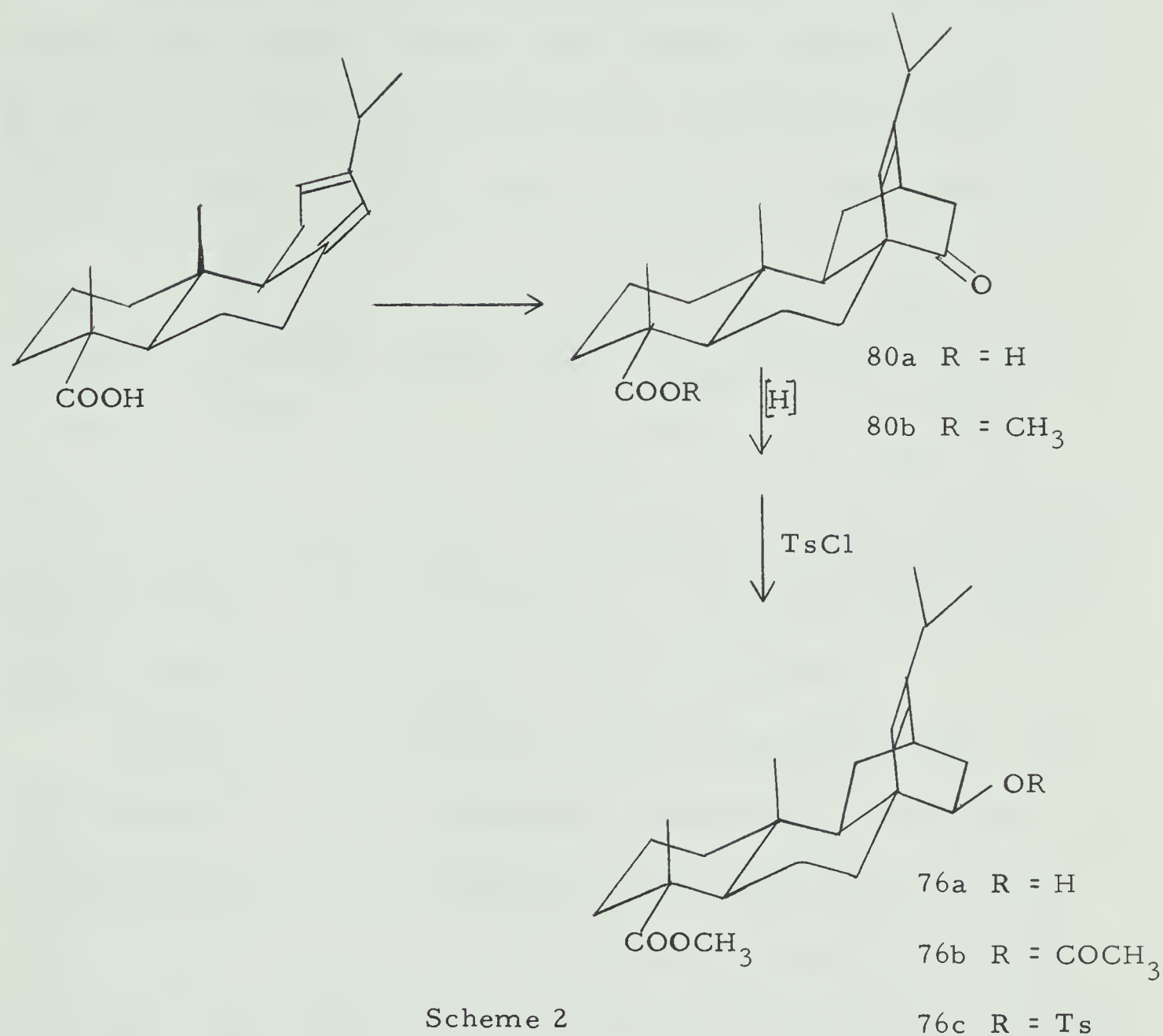
methyl group. Attempts to open the ketal 79 were not successful.

Compound 79 provides an example of intramolecular ketalization of a ketone by an epoxide. There are known instances⁶⁵ of intermolecular ketal formation by reaction of an epoxide with a ketone under the influence of Lewis acid catalysis. The epoxide 78 apparently does not require a catalyst for the intramolecular reaction; or is catalyzed by HCl formed from CHCl_3 . A possible pathway by which compound 79 could be derived from the epoxide 78 is indicated below.



Preparation of Tosylate 76c via the Levopimaric Acid-Acetoxyacrylonitrile Adduct.

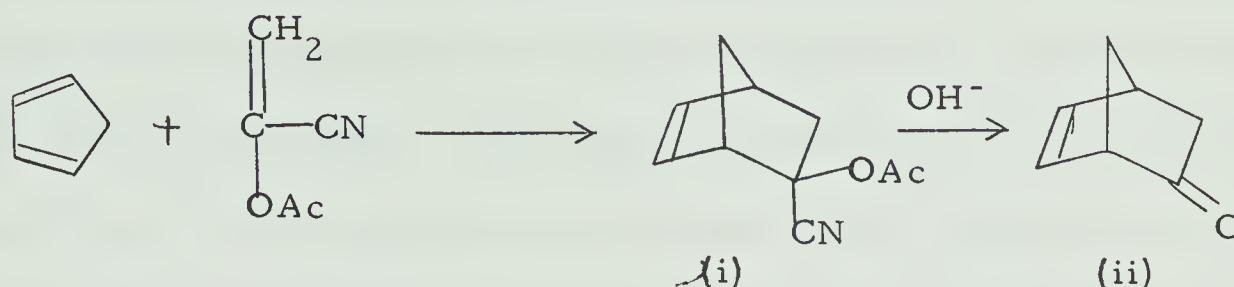
An alternative approach to the synthesis of tosylate 76c is indicated in scheme (2).



The first step in this scheme involves the preparation of keto-acid 80a from levopimaric acid. The subsequent steps required to transform the compound 80a to tosylate 76c are straightforward. The ketoacid 80a can be visualized as a cycloaddition product of levopimaric acid and ketene. However ketene does not act as a dienophile in the Diels-Alder reaction. However, cycloaddition of a ketene moiety can be indirectly effected by using acetoxyacrylonitrile as the dienophile*.

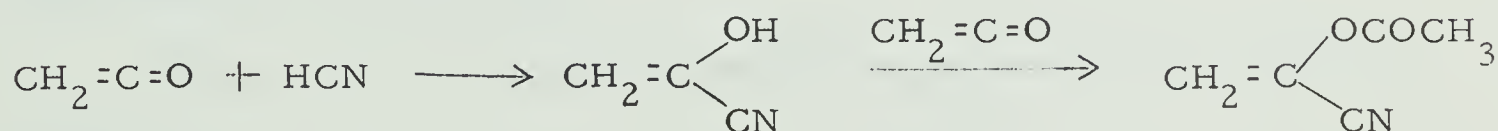
* We are indebted to Professor J. Hooz of this department for suggesting this method.

Bartlett⁶⁶ appears to be one of the first to have used this substance in a Diels-Alder reaction. Thus he had reported, preparation of bicyclo-[2.2.1] heptenone (ii) from cyclopentadiene and acetoxyacrylonitrile. The first product of the Diels-Alder reaction is the cyano acetate (i).



On alkaline hydrolysis (i) gives a cyanohydrin intermediate which loses hydrogen cyanide to form the ketone (ii). A sequence of this type was used successfully in the preparation of the ketoacid 80a.

Acetoxyacrylonitrile is not a readily available substance. An early method^{67a, b} for the preparation of this compound involves reaction between hydrogen cyanide and ketene under the influence of a base such as diethylamine. In the initial step a molecule of ketene presumably reacts with a molecule of hydrogen cyanide to form a cyano-hydrin intermediate. Addition of another molecule of ketene to this

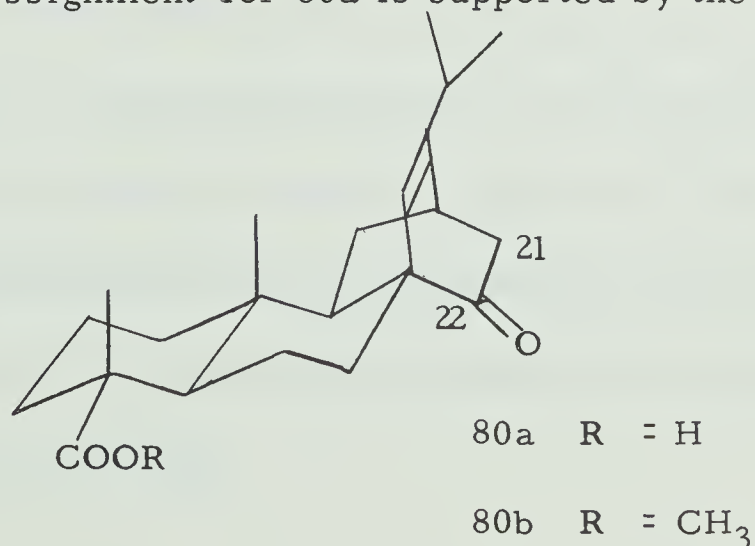


gives acetoxyacrylonitrile. This method* was used for the preparation of acetoxyacrylonitrile in the present work.

* Recently Nowak has reported a more satisfactory method for the preparation of acetoxyacrylonitrile. This involves a reaction of chloroacetaldehyde with cyanide ion. See R. M. Nowak, J. Org. Chem. 28, 1182 (1963).

A toluene solution of levopimaric acid containing an excess of acetoxyacrylonitrile and a few crystals of hydroquinone was heated under reflux for eight hours. The acidic product was separated from the neutral product by extraction with dilute alkali. The acidic product thus obtained did not show absorption attributable to a cyano group in the infrared spectrum. The spectrum however showed a weak band at 1410 cm^{-1} (scissoring of an active methylene) suggestive of the presence of a ketone. The n.m.r. spectrum of the acidic product showed a methyl group at relatively high field ($\tau 9.25$). From these spectral properties of the acidic product it was inferred that the Diels-Alder reaction had taken place and that the cyano and the acetate groups had been converted to a keto group during the work-up. Isolation of the ketoacid 80a was achieved by use of Girard's T reagent. Crystallization of the product from acetonitrile afforded the ketoacid 80a in ca. 35% overall yield. A further small amount of 80a was obtained by alkaline hydrolysis of the neutral product which apparently is a mixed anhydride (with HOAc) of ketoacid 80a.

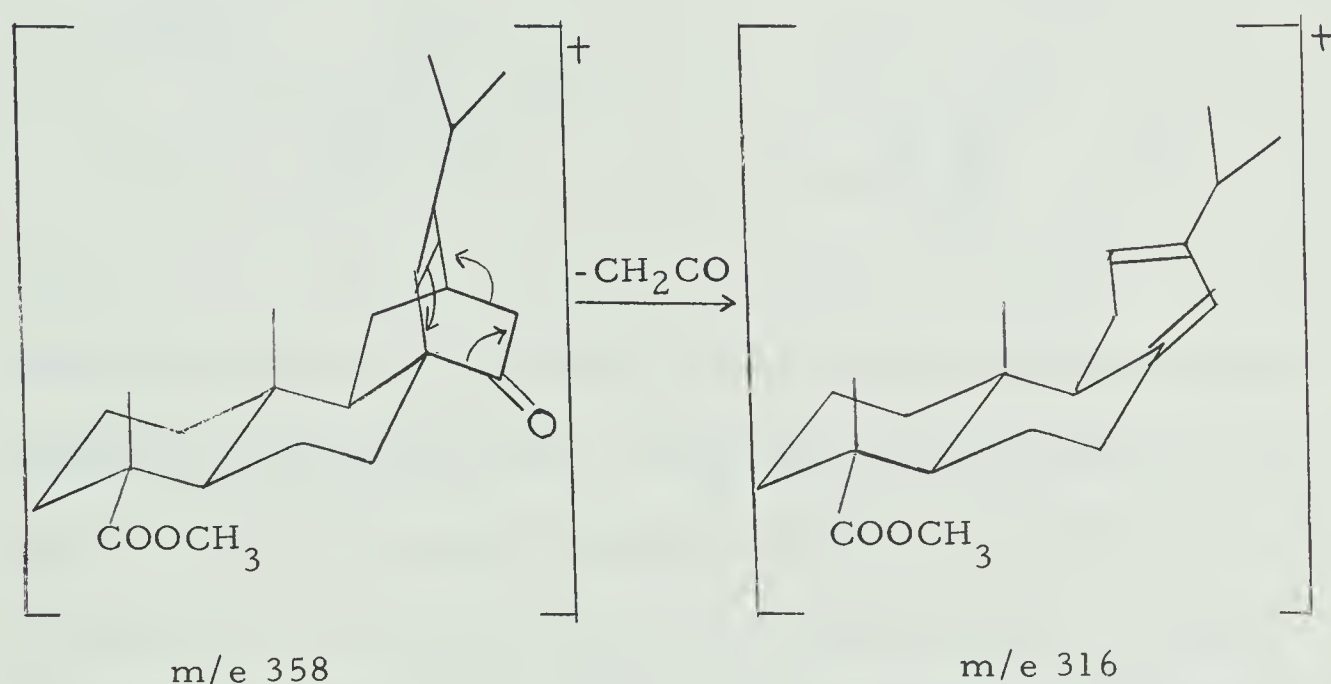
The structural assignment for 80a is supported by the following evidence.



A pure sample (m.p. 195-196°) of ketoacid 80a, obtained by recrystallization from acetonitrile, gave an elemental analysis consistent with the molecular formula $C_{22}H_{32}O_3$ (MW 344). The infrared spectrum shows absorption at 1710-1715 cm^{-1} (br. s) and at 2400-3200 cm^{-1} attributable to a carboxylic group. The band at 1710 cm^{-1} is rather broad due to overlapping of the absorption of a carboxyl and a keto group. The presence of a ketone is indicated by a band at 1410 cm^{-1} (scissoring mode of active methylene). The n.m.r. spectrum of compound 80a is consistent with the assigned structure. It shows four methyl groups attached to saturated carbon atoms. The C-12 methyl, shielded by the Δ^{7-8} double bond, appears at τ 9.25. Compared to the chemical shift of the C-12 methyl group in adduct 31 and amine 29, the chemical shift of this methyl group in compound 80a is lower by ca. 0.10 p.p.m.. This low value can be explained on the basis of a deshielding influence on the C-12 methyl by the C-22 carbonyl. It may be recalled that a C-21 ketone in analogous systems deshielded the C-12 methyl to the extent of ca. 0.05 p.p.m.. Greater deshielding in ketoacid 80a supports the location of the ketone function at C-22. The C-18 methyl groups in compound 80a appear as a six-proton doublet ($J \approx 6.5$ c.p.s.) at τ 8.97 and the C-1 methyl appears at τ 8.83. The presence of a trisubstituted double bond in ketoacid 20 is indicated by the signal at τ 4.72 (C-8 H) and of a carboxyl group by the appearance of a broad signal at τ -1.3 (COOH).

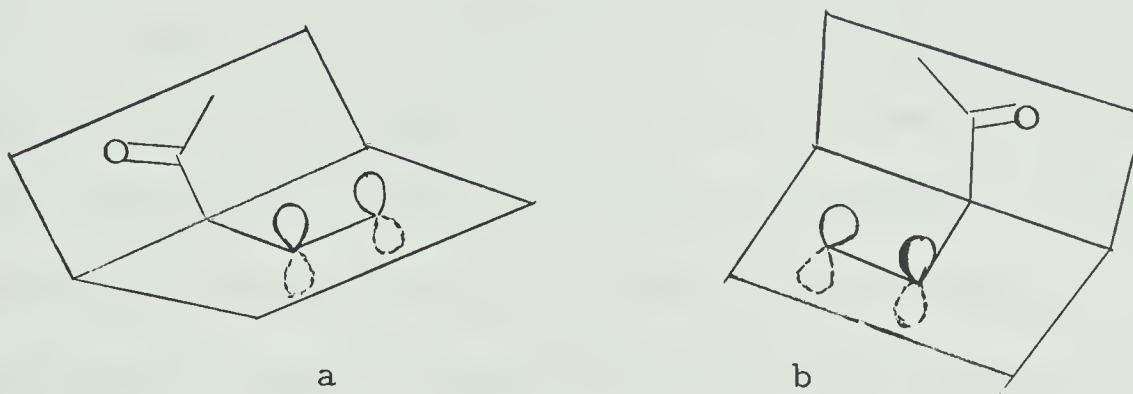
Further support for the structure of ketoacid 80a comes from the spectral properties of the methyl ester 80b obtained by treatment with ethereal diazomethane.

The mass spectrum of the methyl ester 80b (m.p. 83-84°) showed a molecular ion at m/e 358 consistent with the molecular formula $C_{23}H_{34}O_3$. The base peak occurs at m/e 316. This can be rationalized on the basis of the loss of ketene from the parent ion by a reverse Diels-Alder type reaction as shown below.



As in the parent ketoacid 80a the infrared spectrum of the methyl ester 80b shows a strong and somewhat broad band at 1715 cm^{-1} , formed by overlapping of the absorption due to the C-1 carbomethoxy and the C-22 ketone. The presence of a ketone can however be inferred from the band at 1415 cm^{-1} . The n.m.r. spectrum of 80b is consistent with the structure proposed.

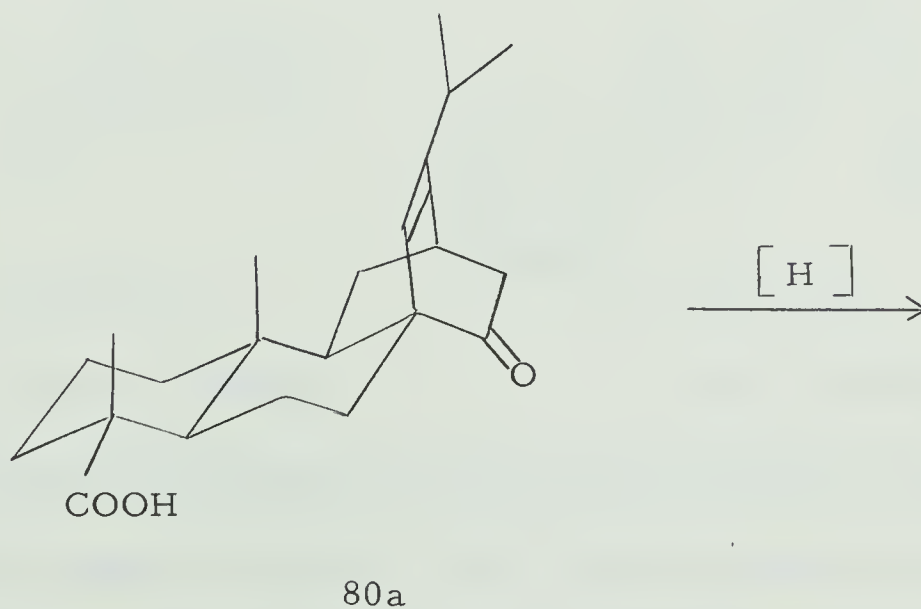
Confirmation of the location of the ketone function at C-22 in ketoacid 80a comes from consideration of its rotatory dispersion curve. The configuration of a β,γ unsaturated ketone can be determined from the sign of the Cotton effect in its r.d. curve, which depends on the geometric arrangement of the β,γ unsaturated carbonyl system⁶⁸. The two possible arrangements for such a system are shown in a and b. An arrangement of the type indicated in (a) gives rise to a negative

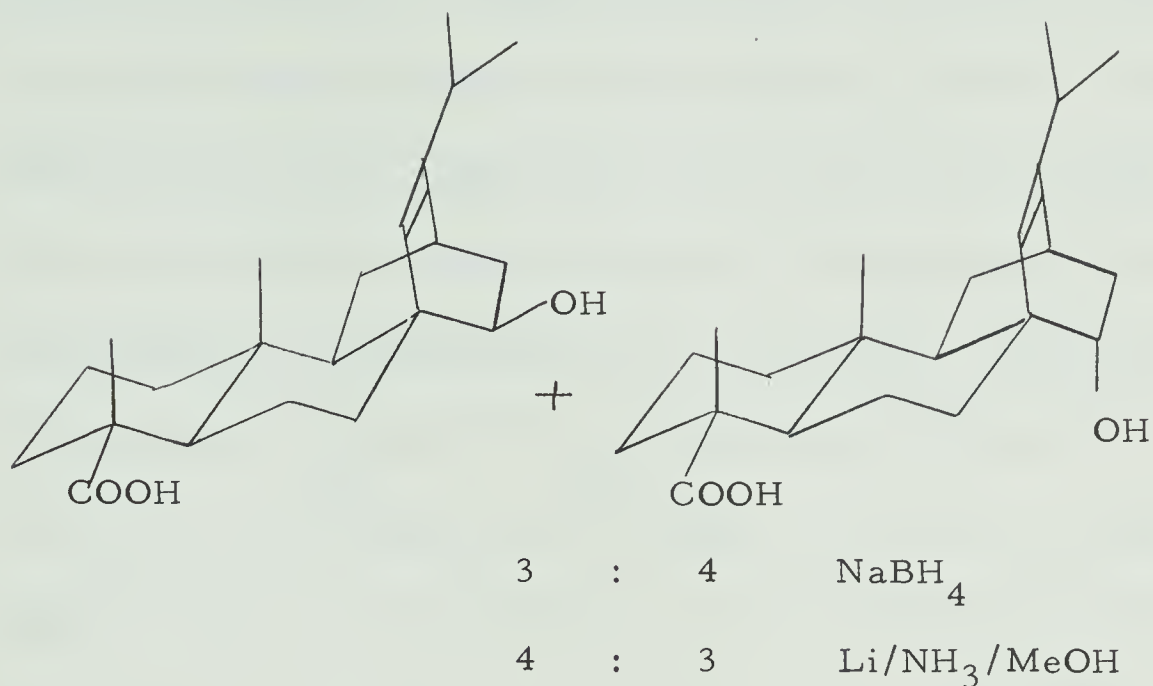


Cotton effect curve and that of the type indicated in (b) gives rise to a positive Cotton effect curve. Application of this criterion to ketoacid 80a leads to the prediction that a positive Cotton effect curve will be observed. In actuality ketoacid 80a indeed showed a strongly positive Cotton effect thus confirming the location of the keto group at C-22 in structure 80a.

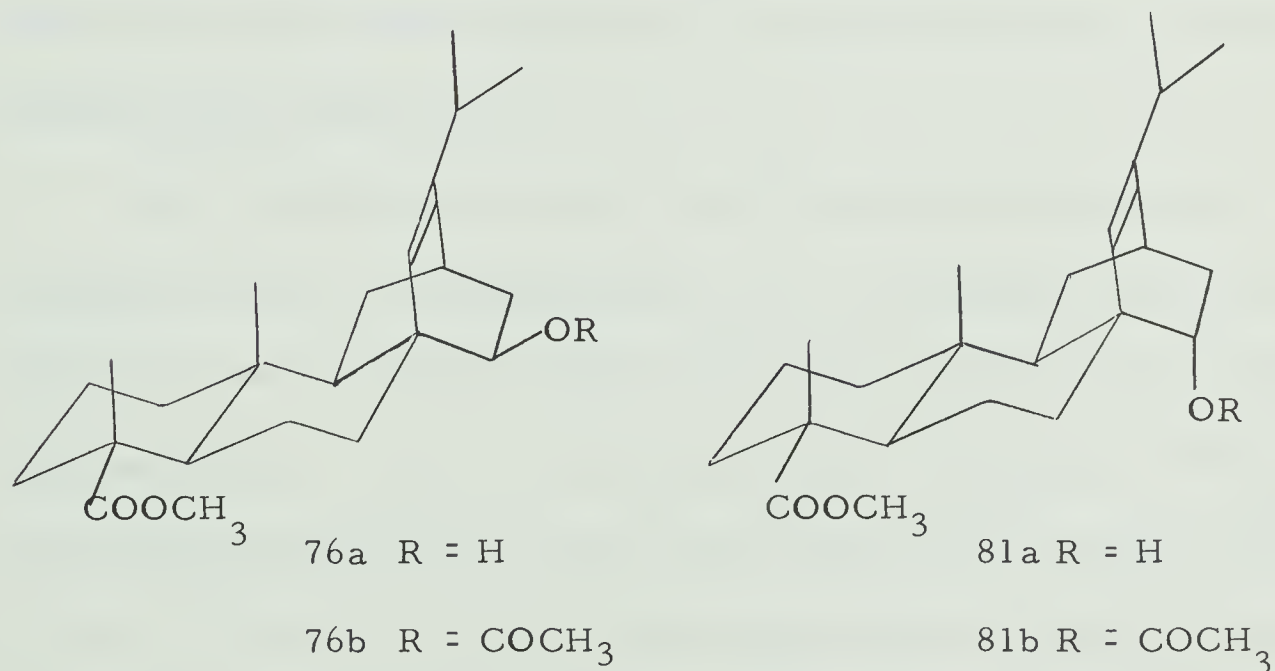
The next step in Scheme 2 involved reduction of the ketone group in ketoacid 80a. Initially this was done with sodium borohydride. A mixture of hydroxy acids epimeric at C-22 was obtained. In order to determine the relative proportions of the two epimers the n.m.r. spectrum of the product, obtained by successive treatment of the

mixture of hydroxy acids with diazomethane and $\text{Ac}_2\text{O/py}$, was determined. The spectrum showed two signals at τ 7.94 and τ 8.08 (in a ratio of 4:3) attributable to the C-22 acetoxy groups. It seemed reasonable to attribute the signal at τ 8.08 to a acetoxy group in an endo position (shielding by the Δ^{7-8} double bond) and the signal at τ 7.94 to a C-22 acetoxy in an exo position. It thus appeared that reduction of 80a with sodium borohydride resulted in the formation of C-22 exo and C-22 endo hydroxy compounds in a ratio of about 4:3. In the hope of obtaining the C-22 endo hydroxy compound in better yield ketoacid 80a was subjected to reduction⁶⁹ with $\text{Li/NH}_3/\text{MeOH}$. Consideration of the relative thermodynamic stabilities of the C-22 exo and the C-22 endo hydroxy compounds leads to the prediction that the formation of the endo isomer should be favored. The product obtained from the reduction of ketoacid 80a with $\text{Li/NH}_3/\text{MeOH}$ was comprised of the C-22 endo and C-22 exo hydroxy compounds in a ratio of about 4:3.





The mixture of hydroxy acids that resulted by reduction of keto-acid 80a with $\text{Li/NH}_3/\text{MeOH}$ was treated with ethereal diazomethane to obtain a mixture of the hydroxy esters 76a and 81a. Chromatographic



separation of the two compounds 76a and 81a was attempted using first silica gel and then alumina columns. The separation was not satisfactory. A circuitous but efficient procedure involving chromatography of the mixture of acetates 76b and 81b was developed for separating the

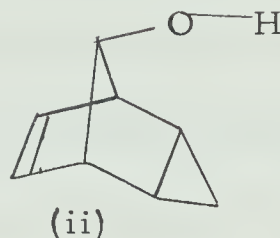
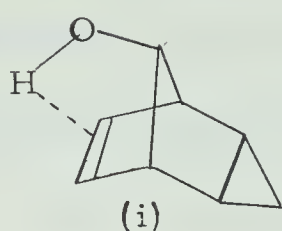
alcohols 76a and 81a. Unlike the alcohols 76a and 81a, the acetates 76b and 81b could be separated on an alumina column. The exo acetate 81b elutes before the endo acetate 76b in the chromatography. The fact that the isomer of higher R_f value is the exo acetate 81b is supported by the spectral characteristics of the compound. The infrared spectrum shows bands at 1370 cm^{-1} (m, δ s OCOCH_3), 1640 cm^{-1} (w, $\text{C}=\text{C}$), 1720 cm^{-1} (br., s, $\text{OC}-\overset{\text{O}}{\parallel}\text{CH}_3$ and $-\overset{\text{O}}{\parallel}\text{C}-\text{OCH}_3$). The n.m.r. spectrum shows signals for the four methyl groups on saturated carbon atoms at τ 9.37 (C-12 Me), τ 9.017 (6H, d., $J=6$ c.p.s., C-18 methyls), and τ 8.86 (C-1 Me). The signal characteristic of the C-22 exo acetoxy group appears at τ 7.94 and the proton geminal to the acetoxy group gives a signal (d. of d., $J = 9$ and 3 c.p.s.) at τ 5.84. The signals at τ 4.72 (1H) and τ 6.36 are attributed to the C 8 proton and the C-1 carbo-methoxy group respectively.

The isomer which comes later in the chromatography is recognized as the C-22 endo acetate 76b. Two signals in the n.m.r. spectrum of this compound clearly distinguish it from the exo isomer discussed above. The C-22 acetoxy group in 76b appears at τ 8.08 and the proton geminal to the acetoxy group gives rise to a signal at τ 5.44 (d. of d., $J = 8$ and 3 c.p.s.). It is significant that the C-22 proton in the exo acetate 81b resonates at higher field than the C-22 proton in 76b by ca. 0.4 p.p.m.. This is in keeping with the general observation⁴³ that the endo protons in a bicyclo $[2.2.2]$ octene system appear at higher

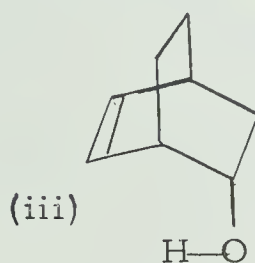
field than the corresponding exo protons. The other n.m.r. data for acetate 76b are comparable to those of the compound 81b and need no comment.

The alcohol 76a was obtained from the acetate 76b by refluxing the latter in a methanolic solution of potassium hydroxide. A small fraction of the C-1 ester also underwent hydrolysis to form the acid which was converted to the ester by treatment with ethereal diazomethane. The structure assigned to alcohol 76a is supported by the following data.

Elemental analysis of a pure sample (m.p. 92-93°, crystallized from Skellysolve B) is consistent with the molecular formula $C_{23}H_{36}O_3$ (MW 360). The infrared spectrum shows broad absorption at 3570 cm^{-1} attributable to a hydroxyl group. It is noteworthy that the infrared spectrum of the corresponding exo alcohol shows a sharp band at 3590 cm^{-1} due to the hydroxyl group. The difference in the absorption due to the hydroxyl in the two compounds can be rationalized in terms of OH to π hydrogen bonding in the endo alcohol 76a. It has been reported⁷⁰ that a hydroxyl group can be intramolecularly H-bonded to a carbon carbon double bond if the two are favorably located in the molecule. An example⁷¹ of an intramolecularly π -H bonded hydroxyl group is provided by compound (i) which shows absorption due to the hydroxyl group at 3576 cm^{-1} . The hydroxyl group in compound (ii) absorbs at 3590 cm^{-1} . Similar π -H bonding is observed^{21b} in the compound



(iii). Evidently the lower frequency at which the hydroxyl group in 76a



absorbs in the infrared is due to intramolecular π -H bonding. Since such hydrogen bonding is possible only if the C-22 hydroxyl group is endo-oriented this supports the assigned stereochemistry of the hydroxyl group in 76a. It is interesting to note that the endo alcohol elutes before the exo alcohol on chromatography on alumina whereas the exo acetate comes ahead of the endo acetate on chromatography on the same adsorbent. Apparently the hydroxyl in the exo alcohol is available for adsorption on the surface of alumina to a larger extent than the corresponding hydroxyl group in the endo alcohol 76a (intramolecular H-bonding in the endo alcohol).

The n.m.r. spectral data for the alcohol 76a are consistent with the assigned structure. With the exception of the position of the signal due to the C-22 H, and the absence of the signal due to an acetoxy group the n.m.r. data for 76a are comparable to those of 76b. The C-22 H in compound 76a appears at τ 6.64, which is about 1.2 p.p.m. upfield

from the signal due to the C-22 H in acetate 76b. A difference of this magnitude in the chemical shifts of the C-22 proton is expected when the geminal acetoxyl group is replaced by a hydroxyl group.

Alcohol 76a was transformed to the tosylate 76c by treatment with p-toluenesulfonyl chloride in pyridine (r.t., 80-90 hrs.). The transformation was quantitative. The formation of tosylate 76c was confirmed by the spectroscopic properties of the product. The presence of a tosyloxy group was deduced from the infrared spectrum which shows bands at 1175 cm^{-1} (s, $\nu_s\text{ SO}_2$), 1350 cm^{-1} (s, $\nu_{as}\text{ SO}_2$), 1600 cm^{-1} (m, aromatic). Further support for the presence of a tosylate group in the product comes from the n.m.r. spectrum. The methyl group on the aromatic ring appears at τ 7.60 and the four aromatic protons give a characteristic A_2B_2 pattern centred at τ 2.53 ($J_{AB} \approx 8$ c.p.s.). The C-22 proton gives a doublet of doublets ($J = 8$ and 2.5 c.p.s.) at τ 5.66. The other n.m.r. data are consistent with the structure 76c. Attempts to crystallize tosylate 76c were not successful. Purification was therefore attempted by chromatography on silica gel. This resulted in the isolation of a compound (82a) free of the tosyloxy group.

Isolation and Characterization of the Diene 82a.

Tosylate 76c was subjected to chromatography on silica gel in the hope of obtaining a pure sample of the tosylate. As soon as a benzene solution (colorless) of the tosylate was transferred to the column

the top portion of the adsorbent became deep purple. Elution of the column with benzene afforded a colorless viscous oil in ca. 70% yield. The oily compound is assigned structure 82a. Discussion concerning this structural assignment will be taken up shortly. Further elution of the silica gel column with ether gave a foam in ca. 15-20% yield. This material on crystallization from Skellysolve-B afforded a crystalline compound which was found to be identical in all respects with the endo alcohol 76a.

Structure 82a for the oily compound is based on the following evidence.



82a R = CH₃

82b R = H

The mass spectrum of compound 82a shows a molecular ion at m/e 342 consistent with the molecular formula C₂₃H₃₄O₂.

The infrared spectrum does not show absorption attributable to a tosyloxy group. The C-1 carbomethoxy group gives rise to absorption at 1720 cm⁻¹. The presence of a conjugated diene is indicated by the bands at 1620 cm⁻¹ (w), and 1635 cm⁻¹ (w). Confirmation of the presence

of a conjugated diene comes from the u.v. spectrum which shows absorption at $258 \text{ m}\mu$ ($\epsilon_{\text{max}} 18,000$). In agreement with the structure 82a the n.m.r. spectrum shows the presence of only two methyl groups attached to saturated carbon atoms. The signal at $\tau 9.13$ is attributed to the C-12 methyl group and the one at $\tau 8.78$ is assigned to the C-1 methyl group. The single olefinic proton at C-8 appears at $\tau 4.15$. Consistent with their location on an unsaturated carbon atom, the methyl groups at C-18 give signals at $\tau 8.34$ and $\tau 8.28$. Finally, the presence of a carbomethoxy group is indicated by the signal at $\tau 6.36$ in the n.m.r. spectrum.

Further support for the structure 82a comes from the spectral properties of the derivative 82b obtained by hydrolysis of compound 82a with potassium tert-butoxide-dimethyl sulfoxide (abbreviated as KtBD).

Use of KtBD in the hydrolysis of hindered esters has been described⁷² by Chang et al. The success of this reagent in hydrolysis of such esters is presumably due to its ability to effect alkyl oxygen fission.

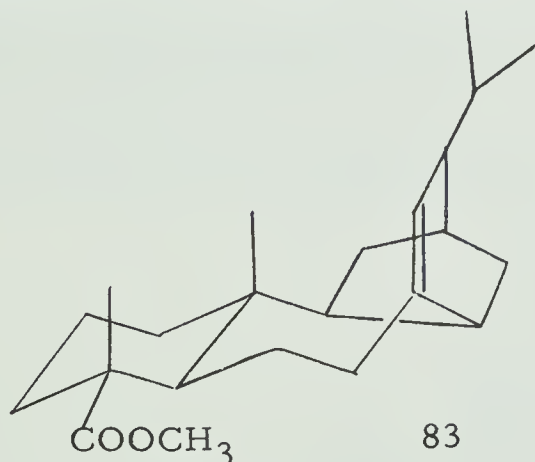
Hydrolysis of the C-1 ester group in 82a was effected by treatment with KtBD for $1\frac{1}{2}$ hours. The acidic product 82b obtained from this treatment showed properties consistent with the assigned structure.

Thus compound 82b gives a molecular ion at m/e 328 in agreement with the molecular formula $\text{C}_{22}\text{H}_{32}\text{O}_2$. The presence of a carboxyl group is indicated by the infrared spectrum which shows bands at

1685 cm^{-1} (with a sh. at 1720 cm^{-1}) and $2400\text{-}3200\text{ cm}^{-1}$ (br). The n.m.r. spectrum of compound 82b is comparable to that of the parent ester 82a. The C-12 and the C-1 methyl groups give signals at $\tau 9.12$ and $\tau 8.77$ respectively. The isopropylidene methyl groups appear at $\tau 8.33$ and $\tau 8.28$. The signal for the olefinic proton on C-8 occurs at $\tau 4.11$.

Compound 82b gave ill-defined crystals on crystallization from acetonitrile. Attempts to obtain an analytical sample by recrystallization led to decomposition of the compound.

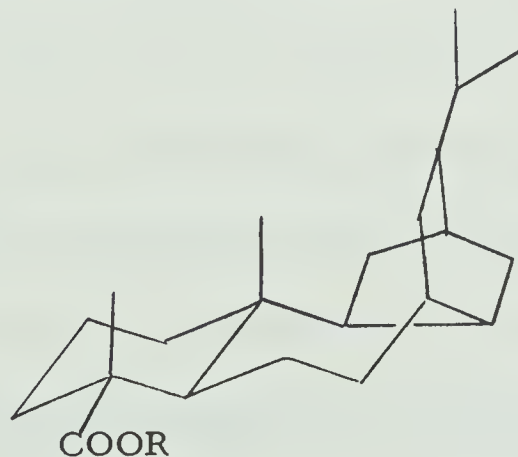
Further support for the structure of the diene 82a comes from the nature of the products obtained on catalytic hydrogenation. An ethanolic solution of diene 82a on catalytic hydrogenation over Pd/C gave predominantly the partially saturated compound 83.



In agreement with the molecular formula $\text{C}_{23}\text{H}_{36}\text{O}_2$ this compound shows a molecular ion at $m/e\ 344$. The presence of an isolated double bond in compound 83 is indicated by the infrared spectrum which shows absorption at 1655 cm^{-1} (w). The C-1 carbo-methoxyl gives rise to a band at 1715 cm^{-1} . The n.m.r. spectrum

of compound 83 shows signals at τ 9.02 and τ 8.80 attributable to the C-12 and the C-1 methyl groups respectively. The saturated nature of C-18 in 83 is indicated by a six proton signal at τ 9.15 (d, $J = 6$ c.p.s.) assigned to the methyl groups on this carbon. The olefinic proton on C-8 appears at τ 4.93, ca. 0.8 p.p.m. higher field than the olefinic proton in diene 82a. The location of the double bond at Δ^{8-14} rather than at Δ^{7-8} is based on the chemical shift of the C-18 methyl groups. It has been observed that the C-18 methyl in compounds (in this series) having a Δ^{7-8} double bond give signals at $\tau \leq 9.0$ in the n.m.r. spectrum. The relatively high chemical shift of the C-18 methyls in compound 83 is indicative of the fact that the double bond is remote enough not to cause a deshielding effect on them. This consideration favors the location of the double bond at Δ^{8-14} .

Catalytic hydrogenation of the olefin 83 over Adam's catalyst furnished the fully saturated compound 84a.



84a $R = CH_3$

84b $R = H$

In agreement with structure 84a the fully saturated compound

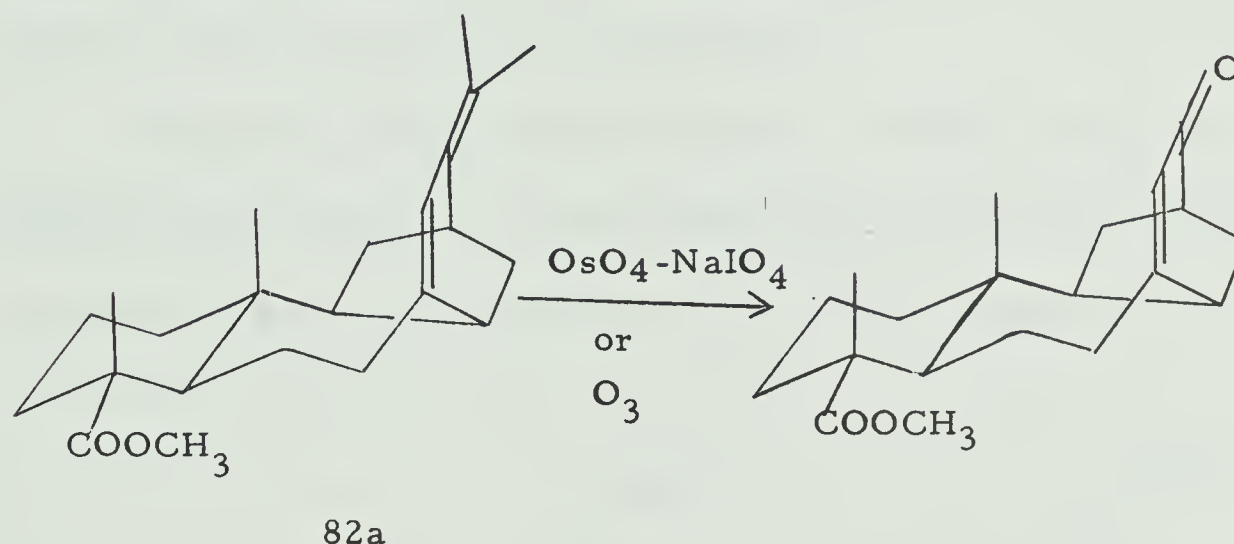
gives a molecular ion at m/e 346 in the mass spectrum. The presence of a carbomethoxyl group is indicated by a band at 1715 cm^{-1} in the infrared spectrum and by a three proton singlet at τ 6.38 in the n.m.r. spectrum. The four methyl groups on saturated carbon atoms appear at τ 9.13 (6H, d., $J=6$ c.p.s., C-18 methyls), τ 8.92 (C-12 methyl) and τ 8.79 (C-1 methyl). In agreement with the fully saturated nature of this compound, the n.m.r. spectrum does not show a signal attributable to an olefinic proton.

A crystalline derivative 84b from compound 84a was obtained by subjecting the former to treatment with KtBD. The spectral properties of 84b are consistent with the assigned structure.

Thus the mass spectrum of a sample (m.p. $128-132^{\circ}$, crystallized from CH_3CN) gives a molecular ion at m/e 332 in agreement with the molecular formula $\text{C}_{22}\text{H}_{36}\text{O}_2$ which was confirmed by exact mass measurement. The carboxyl group in 84b gives rise to absorption at 1690 cm^{-1} (sh. at 1730 cm^{-1}) and $2400-3200\text{ cm}^{-1}$ in the infrared. The n.m.r. spectrum (100 Mc/sec) shows a pair of doublets ($J=6$ c.p.s.) at τ 9.14 and τ 9.13 attributed to the C-18 methyls which are rendered nonequivalent due to the asymmetric environment at C-7. The C-12 and the C-1 methyl groups appear at τ 8.88 and τ 8.76 respectively. It may be recalled that the chemical shifts of the C-methyls in 84b are comparable to those in the N-acetates 63, 64 and the sulfonamides 66, 67. This appears to be a characteristic feature of the saturated

compounds with a rearranged skeleton.

The tetrasubstituted \triangle^{7-18} double bond in diene 82a appears to be more reactive in catalytic hydrogenation. The sluggishness of the \triangle^{8-14} double bond in this reaction is apparently due to its hindered nature (C-12 methyl group). This suggested the possibility that the isopropylidene group in 82a might be selectively removed by Lemieux-Johnson oxidation^{73a} or by controlled ozonolysis to obtain an α, β unsaturated ketone. The formation of this ketone would not only support



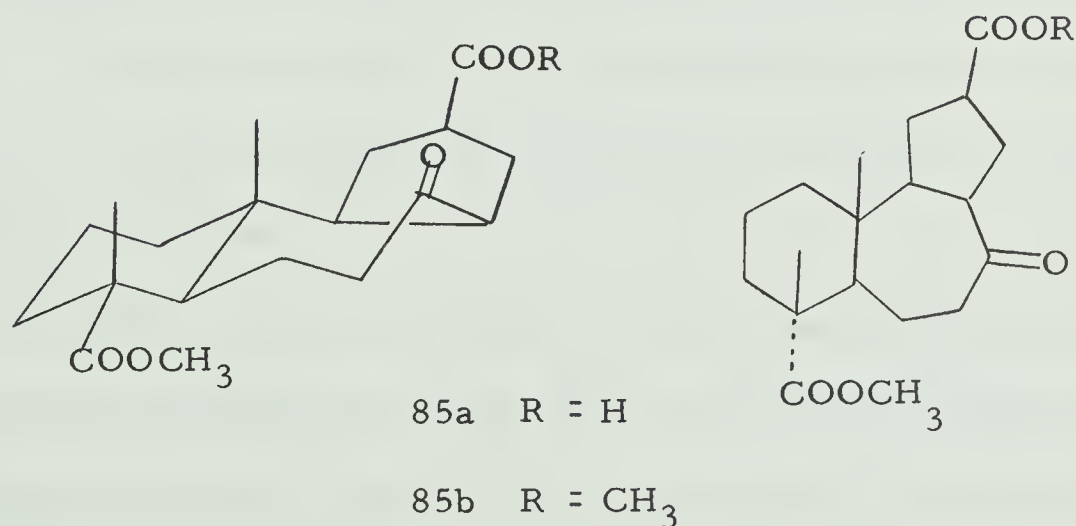
the structure 82a assigned to the diene but will also constitute proof for the structure of ketone 316 isolated in the deamination of amine 29.

With this purpose in mind diene 82a was subjected to reaction with $\text{OsO}_4\text{-NaIO}_4$ following the method of Edwards *et al*^{73b}. The product obtained from this reaction was an intractable mixture.

In an alternative approach the diene 82a was allowed to react with a limited quantity of ozone⁷⁴ (CH_2Cl_2 solution). The acidic fraction

of the product resulting from controlled ozonolysis was removed by extraction with dilute alkali. The neutral fraction thus obtained showed absorption at 1630 cm^{-1} and 1670 cm^{-1} attributable to an α,β unsaturated ketone. The u.v. spectrum showed absorption at $243\text{ m}\mu$. Chromatography of the neutral fraction on silica gel gave material rich in α,β -unsaturated ketone as judged by the infrared spectrum. Further chromatography of the ketone-rich fractions on alumina afforded a crystalline substance (ca. 7% overall yield) which was found to be identical in all respects with an authentic sample of ketone 316. The structure of ketone 316 is thus established.

Complete ozonolysis (ethyl acetate, -70°C) of diene 82a furnished in small amounts a crystalline substance (m.p. $180-193^{\circ}$) whose spectral properties are consistent with the formulation 85a.

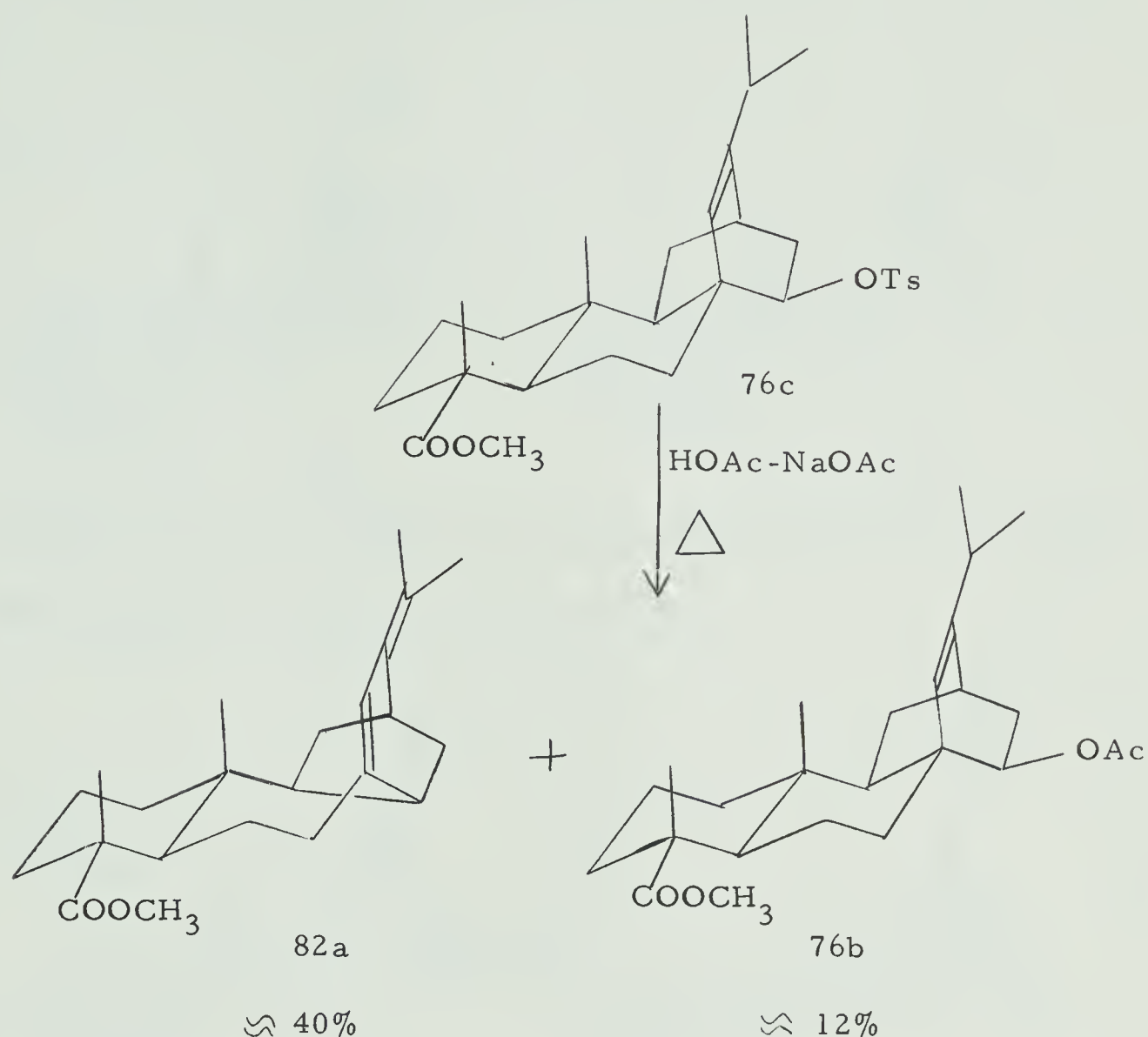


The infrared spectrum shows strong absorption at $1700-1730\text{ cm}^{-1}$ (overlapping of $>\text{C}=\text{O}$, COOH , and COOCH_3) and at $2400-3100\text{ cm}^{-1}$ (br., COOH). The presence of a ketone with an α methylene is inferred

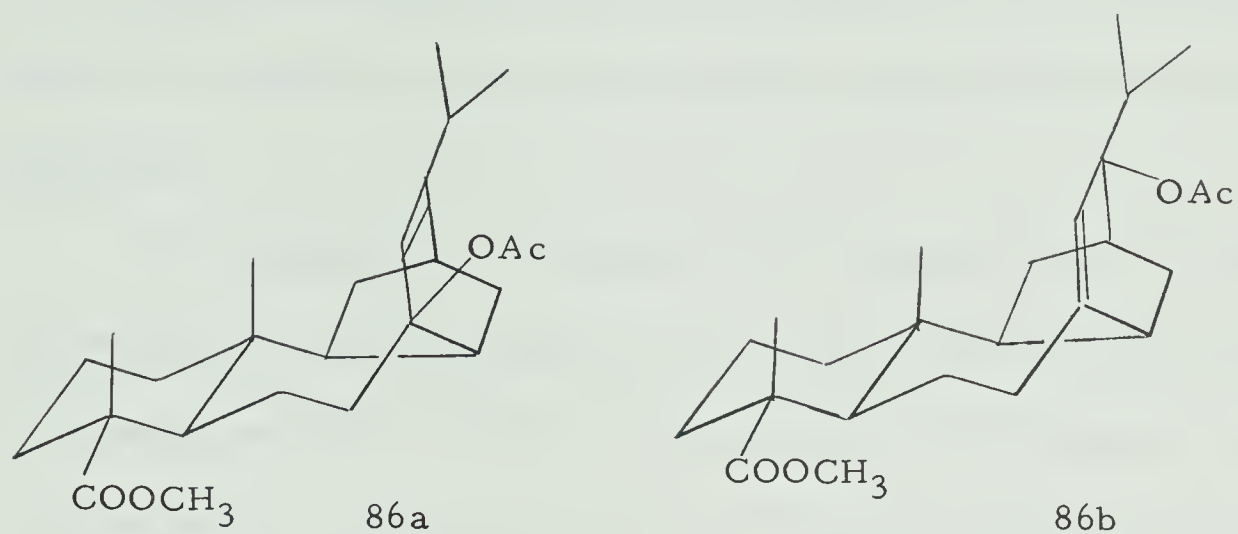
from the presence of a band at 1405 cm^{-1} attributable to the scissoring mode of an active methylene. The molecular weight of 85a was determined mass spectrometrically. Ketoacid 85a was converted to the methyl ester 85b by treatment with ethereal diazomethane. The mass spectrum of 85b showed a molecular ion at m/e 350 consistent with the molecular formula $\text{C}_{20}\text{H}_{30}\text{O}_5$

The formation of diene 82a from tosylate 76c by reaction on silica gel was not expected. This adsorbent was chosen for the chromatographic purification of tosylate 76c since tosylates of bridged ring compounds have been purified in this manner. The elimination of p-toluenesulfonic acid with concurrent rearrangement of the bicyclo-[2.2.2]octane system to the bicyclo[3.2.1]octane system on silica gel constitutes a simple and efficient method for gaining entry into the partial skeleton of lycoctonine type alkaloids from an atisine type skeleton. Selective cleavage of the isopropylidene group in diene 82a affords a C-19 skeleton identical with that of the ABCD part of the lycoctonine type bases.

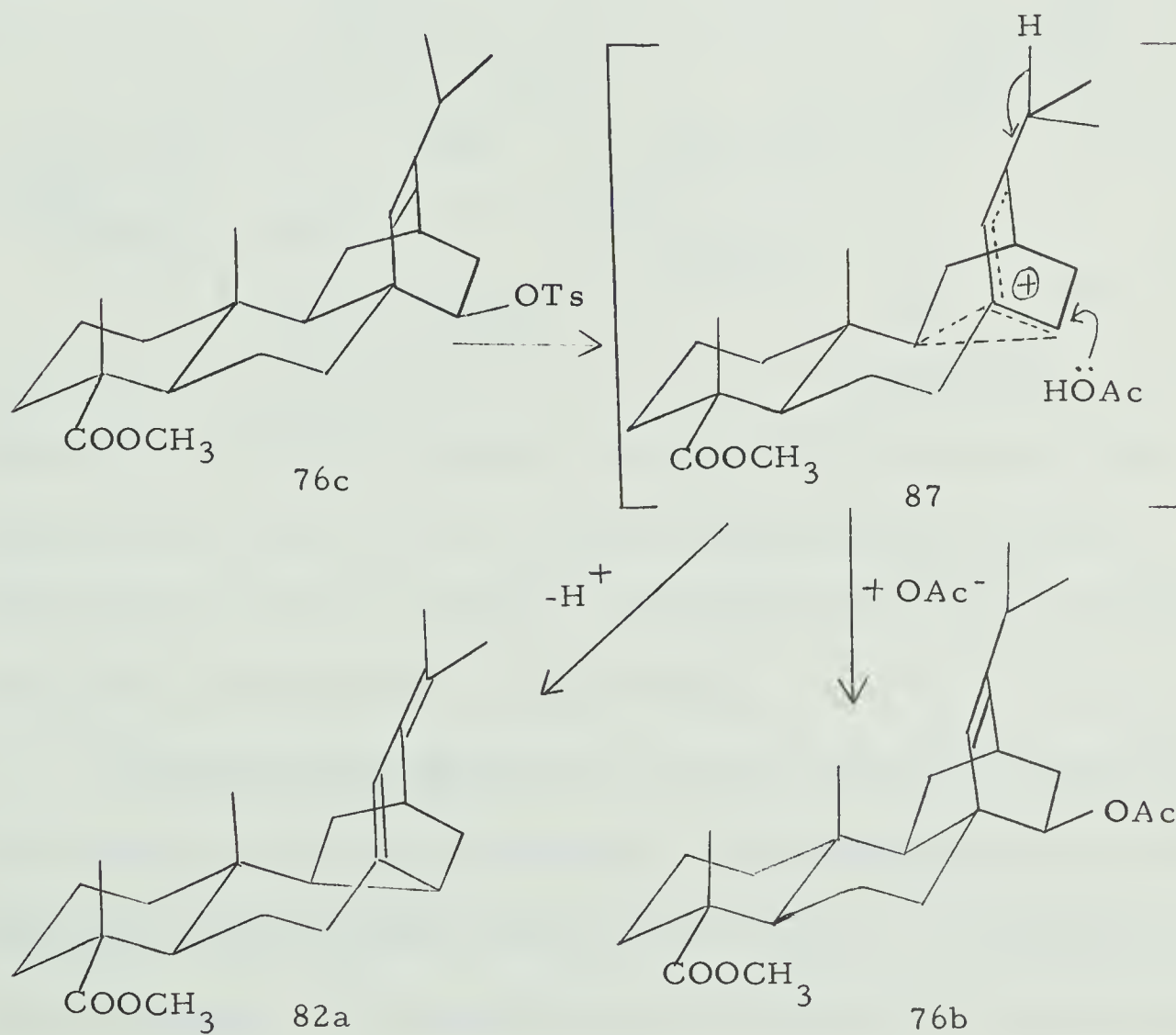
In order to determine whether the rearrangement of tosylate 76c is specifically brought about on the surface of the adsorbent or whether it is of general nature, tosylate 76c was subjected to acetolysis in glacial acetic acid in the presence of sodium acetate. The product obtained consisted mainly of diene 82a and the endo acetate 76b as judged from the n.m.r. spectrum.



Chromatography of the acetolysis product on alumina afforded diene 82a in ca. 40% yield. The endo acetate 76b was isolated in ca. 12% yield. The n.m.r. spectrum of the acetolysis product indicates the presence of minor amounts of two other acetates. Neither of these could however be isolated in pure form from the chromatography on alumina. Assuming that these acetates possess the structures 86a and 86b their formation in relatively small amounts indicates that they are not the favored products in acetolysis. The favored pathway for the reaction of the intermediate carbonium ion 87 thus appears,

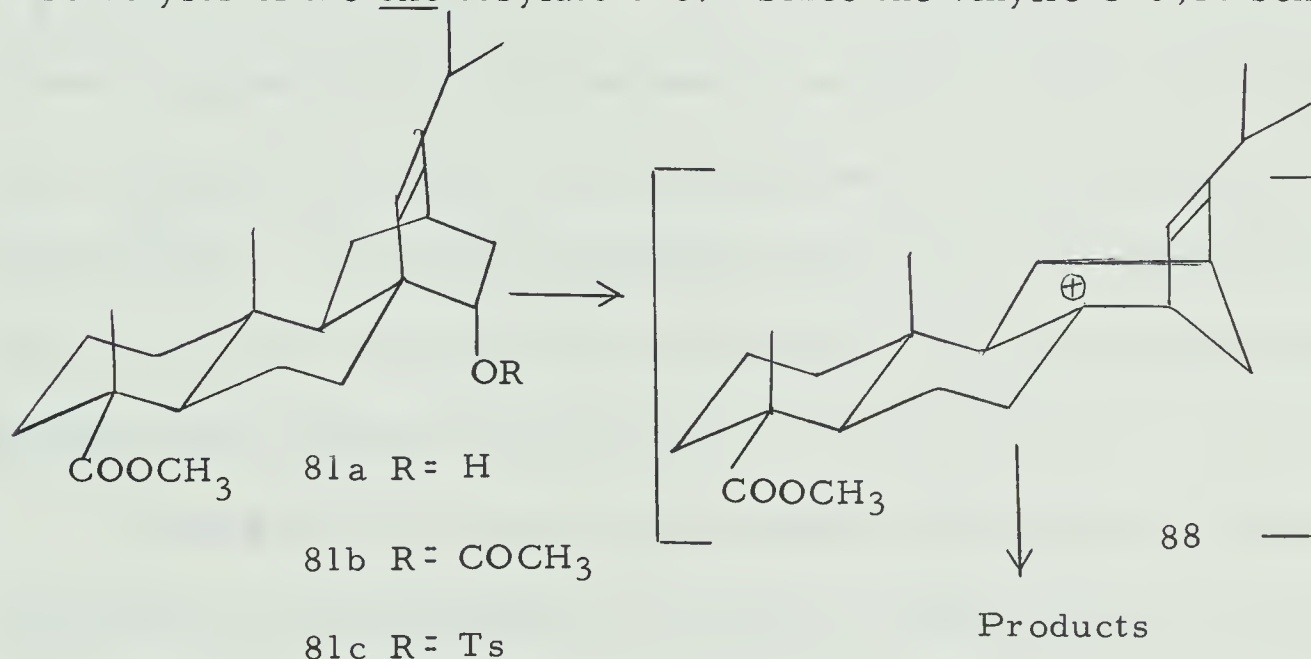


probably for steric reasons, to be elimination of C-18 H to give 82a and nucleophilic attack at C-22 to give 76b.



The discussion of the solvolytic approach will be concluded with a few remarks on the behaviour of the exo alcohol 81a on attempted tosylation.

In the light of the knowledge that the endo tosylate 76c undergoes a stereospecific rearrangement in a solvolytic reaction it was of interest to examine whether a similar stereospecific rearrangement takes place on solvolysis of the exo tosylate 81c. Since the vinylic C-8,14 bond is



sterically well set for migration in tosylate 81c the products from the solvolysis reaction of 81c might be those derivable from the intermediate carbonium ion 88. As the first step in this investigation preparation of tosylate 81c was undertaken.

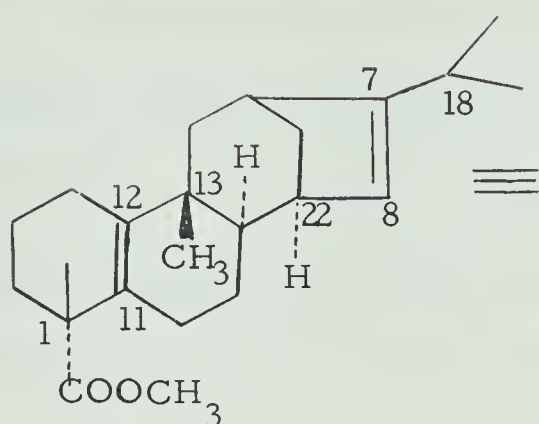
Alcohol 81a was obtained by hydrolysis of the exo acetate 81b with methanolic potassium hydroxide. The infrared spectrum of the hydrolysis product showed a sharp band at 3590 cm^{-1} attributable to a hydroxyl group. The product was used without further purification in the next step. Alcohol 81a was subjected to treatment with p-toluene-

sulfonyl chloride in pyridine as in the case of alcohol 76a and the product was isolated in the usual manner. The infrared spectrum of the product did not show absorption characteristic of a hydroxyl group or of a tosyloxy group. The presence of a carbomethoxyl group was indicated by absorption at 1715 cm^{-1} in the infrared. Surprisingly an absorption band at 1780 cm^{-1} (m), suggestive of the presence of a γ lactone, was also observed. The n.m.r. spectrum of the product showed a signal at τ 4.22 attributable to an olefinic proton but did not show a signal attributable to a proton geminal to a lactone function ($\text{H}-\text{C}-\text{O}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{C}$). The infrared spectrum, the n.m.r. spectrum, and the t.l.c. behavior suggested the presence of two major components, an ester and a lactone, in the mixture.

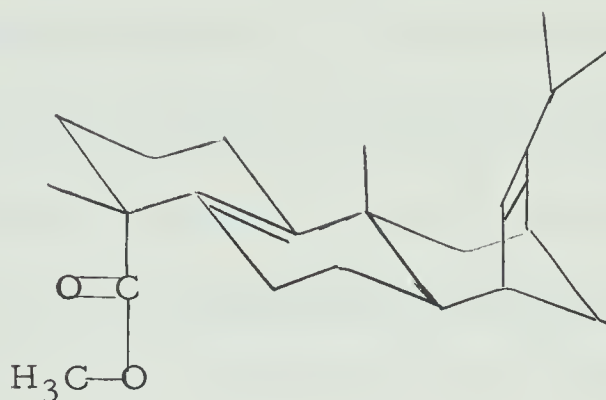
Separation of the ester and the lactone components was initially attempted by chromatography on silica gel. These attempts were not successful. Alternatively, a benzene solution of the mixture was filtered through basic alumina. The lactone was retained and the ester passed through the adsorbent. The lactone was then recovered in the form of a carboxylic acid by extracting the material adsorbed on alumina with $\text{HOAc}-\text{CH}_2\text{Cl}_2$.

Structure 89 is tentatively proposed for the ester on the basis of the following considerations.

The mass spectrum of 89 shows a molecular ion at m/e 342 in agreement with the molecular formula $\text{C}_{23}\text{H}_{34}\text{O}_2$.



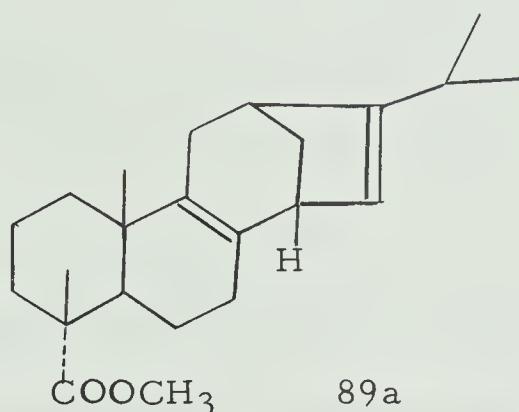
89



89

The infrared spectrum shows bands at 1615 cm^{-1} (w, C=C) and 1710 cm^{-1} (C-1 COOMe). The n.m.r. spectrum of compound 89 is informative. A signal at $\tau 9.17$ is attributed to the C-13 methyl group which lies in the shielding cone of the Δ^{7-8} double bond and at the same time is deshielded by the Δ^{11-12} double bond. The signals at $\tau 8.83$ and at $\tau 6.36$ are assigned to the C-1 methyl group and the C-1 carbomethoxyl respectively. The methyls in the C-7 isopropyl group appear as a pair of doublets ($J \approx 7$ c.p.s.) at $\tau 8.97$ and $\tau 8.98$. The presence of an olefinic proton in 89 is indicated by the signal (br. s.) at $\tau 4.22$. More detail concerning the locations of the C-18 H, C-8 H, and C-22 H was revealed by spin-decoupling experiments. Simultaneous irradiation 488 c.p.s. (at 100Mc/s, $\tau 7.61$) upfield from CHCl_3 caused the pair of doublets at $\tau 8.97$ and $\tau 8.98$ to collapse to a singlet (br.). Concurrently the broad signal at $\tau 4.22$ due to the olefinic proton was transformed into a clean doublet ($J \approx 2$ c.p.s.). Thus the C-18 proton resonates at $\tau 7.61$ (488 c.p.s. upfield from

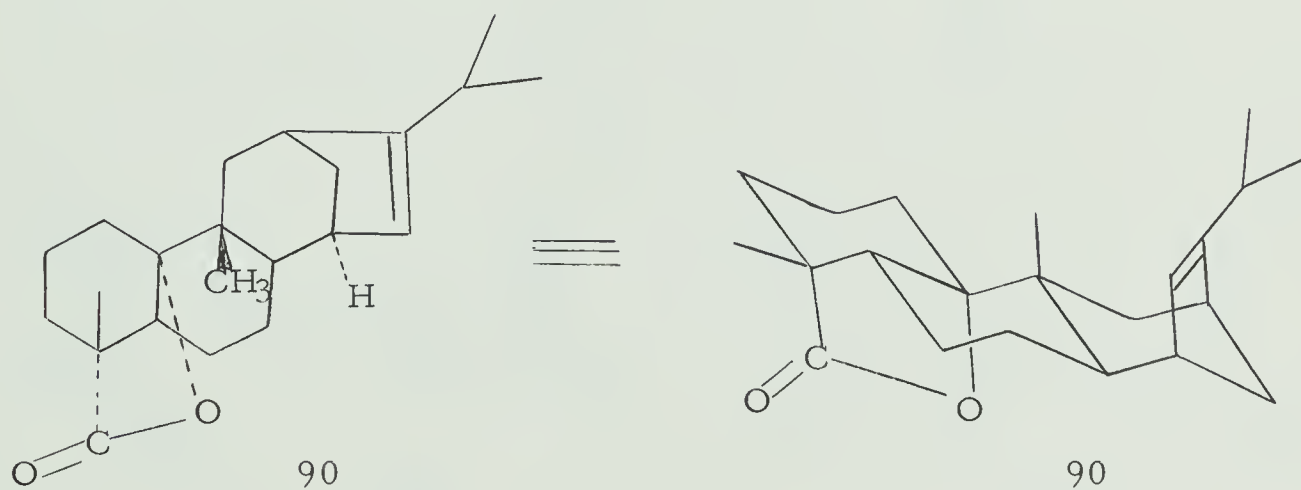
CHCl_3). Simultaneous irradiation 488 c.p.s. (τ 7.61) and 505 c.p.s. (τ 7.78) upfield from CHCl_3 caused the signal at τ 4.22 to collapse to a sharp singlet. The signal for the C-22 proton can thus be located at τ 7.78. The results of the decoupling experiments are consistent with the proposed structure but can not be satisfactorily explained on the basis of the alternate structure 89a. A chemical shift of τ 7.78



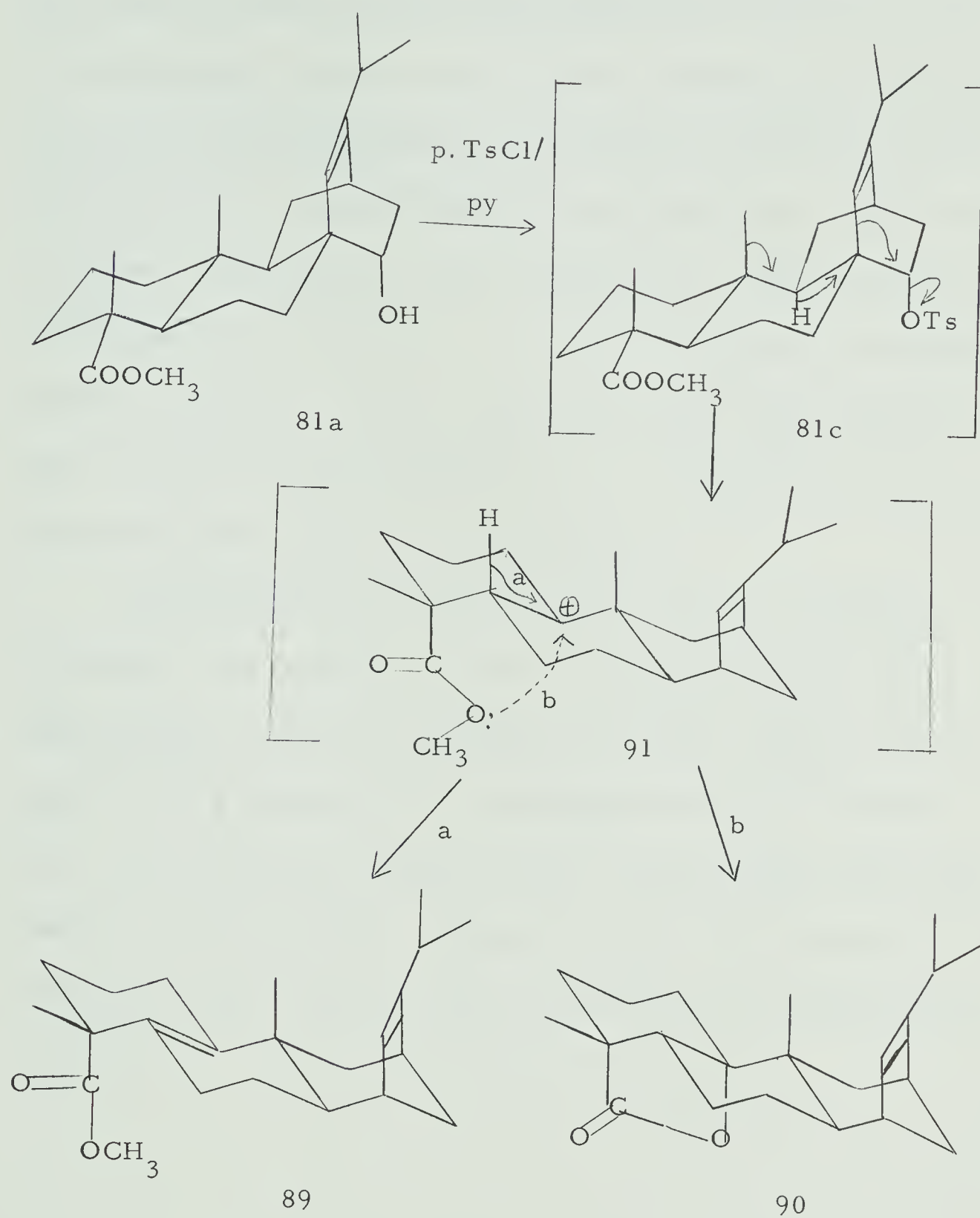
for the doubly allylic proton at C-22 in 89a does not appear likely. The formation of a γ lactone again favors the structure 89 as will be discussed shortly.

Catalytic hydrogenation of an ethanolic solution of 89 over Adam's catalyst gave a product whose infrared spectrum did not show absorption attributable to a carbon-carbon double bond. The n.m.r. spectrum of the hydrogenated product shows the signal attributable to an olefinic proton. The C-13 and the C-1 methyls appear at τ 9.06 and τ 8.87 respectively. The signals due to the methyls in the C-7 isopropyl group are poorly resolved and appear as a broad absorption at τ 9.13. The poor resolution of the signals due to the C-18 methyls may be due to virtual coupling with the C-7 H.

A detailed examination of the lactone component could not be undertaken since it was transformed into a carboxylic acid on the alumina used in the separation and the amount of this acid available was very small. The spectral properties attributable to the lactone are however revealing. The five-membered nature of the lactone ring is indicated by the absorption at 1780 cm^{-1} in the infrared. Closure of the lactone ring at a tertiary carbon is apparent from the n.m.r. spectrum (of the crude product from attempted tosylation of 81a) which shows no signal due to a proton geminal to a lactone function ($-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-\text{C}-\underline{\text{H}}$). The only position available for such a ring closure in a structure such as 81a is at C-12 provided the methyl group on this carbon migrates during the course of the reaction. A mechanistically plausible structure for the lactone is shown in 90.

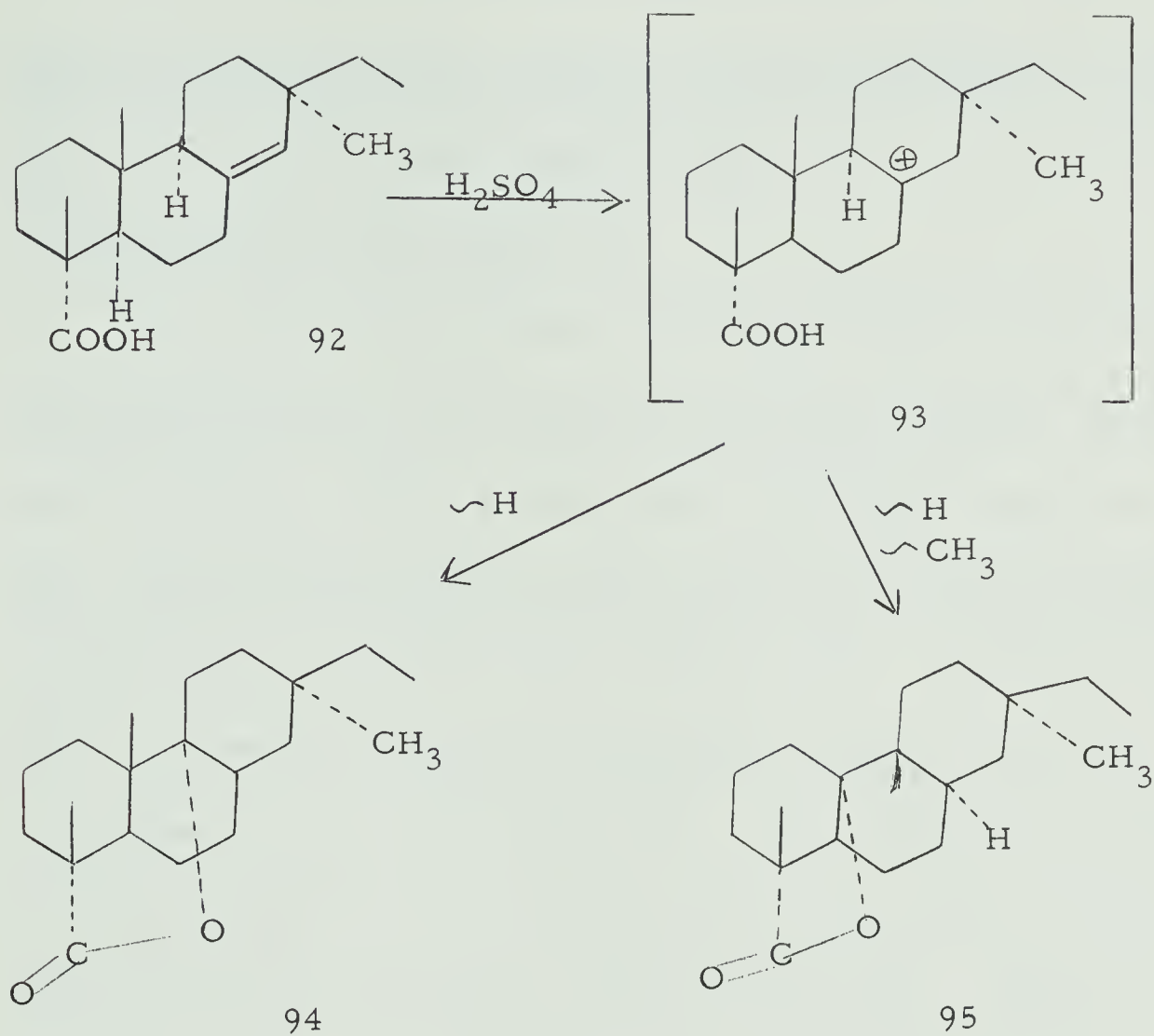


The formation of both ester 89 and lactone 90 may be rationalized in terms of the following scheme.



The reactive tosylate 81c generated from 81a by treatment with p-toluenesulfonyl chloride could form the carbonium ion 91 by loss of the tosyloxy group followed by (or concerted with) migration of the C-13 H and the C-12 Me. Ester 89 and lactone 90 are then formed by pathways indicated by a and b respectively. Whether the C-1 carbomethoxyl or the parent C-1 carboxyl is involved in the lactonization is uncertain. It is not impossible that a small fraction of the C-1 ester in the exo acetate 81b was converted into the acid during hydrolysis of the C-22 acetoxyl group.

Lactonization of the type discussed above is not without precedent. The isolation of 5- and 6-membered lactones from dihydropimaric acid (92) on treatment with conc. sulfuric acid is reported in the literature⁷⁵. Protonation of the \triangle^{8-14} double bond in dihydropimaric acid (92) leads to the formation of the intermediate carbonium ion 93. Migration of the C-13 H and the C-12 methyl followed by closure of the lactone ring at C-12 gives rise to



compound 95. Formation of lactone 90 is analogous.

EXPERIMENTAL

PREPARATION AND REACTIONS OF THE LEVOPIMARIC ACID - METHYL VINYL KETONE ADDUCT (77a).

a) Preparation of the adduct 77a.

A solution of levopimaric acid (12 g), methyl vinyl ketone (20 ml) and hydroquinone (0.2 g) in benzene (50 ml) was refluxed on the steam bath for 8 hours. Excess methyl vinyl ketone and solvent were removed under reduced pressure, the residue dissolved in 100 ml of benzene and washed with water till free of the hydroquinone. The benzene solution was then dried over anhydrous magnesium sulfate, filtered and evaporated to give a white foam (14 g). The white foam was dissolved in 100 ml acetone, 6 ml of cyclohexylamine added and the white solid that precipitated was filtered, washed with acetone, and dried, to afford 13 g of the cyclohexylamine salt. A suspension of this salt in ether (200 ml) was shaken with 10% phosphoric acid (50 ml) in a separatory funnel. The aqueous acidic layer was removed, the ether solution washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a white foam (10.5 g). Crystallization of the white foam from acetonitrile provided 8 g of adduct 77a (\approx 55%). The crystalline compound, m.p. 135-136°, had the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3200-2400 (broad), 1700 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ = 9.38 (3H), 8.95 (6H, d., $J \approx 6.5$ c.p.s.), 8.86 (3H), 8.07 (3H), 4.58 (1H), -0.75 (1H, broad).

Esterification of adduct 77a with ethereal diazomethane provided the oily methyl ester 77b. Infrared spectrum: $\bigcup_{\text{max}}^{\text{CCl}_4}$ 1730 (s), 1700 (m), 1360 cm^{-1} (m). Nuclear magnetic resonance spectrum: $\tau = 9.40$ (3H), 8.95 (6H, d., $J = 6.5$ c.p.s.), 8.87 (3H), 8.08 (3H), 6.36 (3H), 4.55 (1H). Mass spectrum: m/e 386 (molecular ion, 3), 316 (39), 301 (38), 43 (100).

b) Oxidation of adduct 77a with sodium hypobromite.

The oxidizing reagent was prepared by adding bromine (0.65 ml, 2 mmoles) to an ice-cold aqueous solution (8 ml) of sodium hydroxide (1.86 g, 46 mmoles).

Adduct 77a (157 mg) was added in small portions with stirring to the above solution of sodium hypobromite and the reaction mixture kept stirred overnight. Excess reagent was destroyed by adding a solution of sodium sulfite. The alkaline solution was acidified with conc. HCl and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to give a white foam (165 mg). This was esterified with ethereal diazomethane and a portion (140 mg) of the esterified material was chromatographed on neutral alumina (7 g of activity II). Elution with benzene (90 ml) gave 58 mg of an unidentified material. Further elution with the same solvent (90 ml) gave a white foam (15 mg) which crystallized from methanol. The infrared spectrum of the crystalline substance (m.p. 186-189^o) was superimposable upon that of an authentic sample

(m.p. 191-192°) of the isopropylidene lactone 39. Continued elution with benzene-ether (19:1) gave a crystalline substance (10 mg). Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1775 (s, γ_{lactone}), 1730 (s), 1610 (w), 990 cm^{-1} (m). The exact nature of this substance was not determined.

c) Attempted Baeyer-Villiger oxidation of the ketoester 77b.

A solution of ketoester 77b (105 mg, 0.27 mmoles) and m-chloro-perbenzoic acid (69 mg, 0.4 mmoles) in dry benzene (15 ml) was allowed to stand in the dark at room temperature. The reaction was monitored by infrared spectroscopy. The aliquots, withdrawn after every 48 hours, were diluted with ether, treated with aqueous sodium sulfite, shaken with dilute sodium carbonate, dried over anhydrous magnesium sulfate and evaporated. The samples thus obtained were used for determining the infrared spectra. The intensity of the band at 1700 cm^{-1} ($-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_3$) diminished slightly in the first 144 hours and then remained substantially unchanged. After 12 days the reaction mixture was worked up as for the aliquots and a white foam (63 mg) was obtained. This foam possessed the following spectral characteristics. Infrared spectrum: $\nu_{\text{max}}^{\text{CCl}_4}$ 1735 cm^{-1} (s), 1700 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.28 (3H, d., $J \approx 7.5$ c.p.s.), 9.19 (3H), 8.94 (3H, d., $J \approx 7.5$ c.p.s.), 8.85 (3H), 7.98 (3H), 6.9 (1H), 6.37 (3H). The solution used to measure the n.m.r. spectrum was evaporated to dryness and allowed to stand for several days at room temperature. During this period the glassy solid crystallized. The crystalline substance, ketal 79, was

isolated by dissolving the noncrystalline material in Skellysolve B-ether (1:1) and pipetting off the solution. Ketal 79 (m.p. 149-150°) possessed the following spectral characteristics. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ 9.06 (6H, d., $J \approx 7$ c.p.s.), 9.04 (3H), 8.84 (3H), 8.50 (3H), 6.37 (3H), 5.90 (1H). Mass spectrum: m/e 402 (molecular ion, 69), 331 (45), 43 (100).

Ketal 79 (10 mg) was refluxed for 6 hours in aqueous acetone (5:1, 6 ml) containing p-toluenesulfonic acid (5 mg). The acetone was evaporated, the residue diluted with water and extracted with ether. The ether extract was washed with dilute sodium bicarbonate, then water, and dried over anhydrous magnesium sulfate, filtered and evaporated to give unchanged starting material.

e) Attempted Baeyer-Villiger reaction of ketoester 77b with monoperphthalic acid.

Monoperphthalic acid was prepared by the procedure described in "Organic Synthesis" 42, 77 (1962).

A solution of ketoester 77b (409 mg) in ether (10 ml) was added with stirring to an ice-cold solution of monoperphthalic acid (20 ml) and the resulting solution was stored in the refrigerator for three weeks. The solution was then treated with dilute sodium sulfite, washed with dilute sodium carbonate, dried over anhydrous magnesium sulfate and evaporated. The product thus obtained, possessed spectral properties similar to those displayed by the product obtained by m-chloroper-

benzoic acid treatment.

PREPARATION OF THE TOSYLATE 76C.

a) Preparation of the adduct 80a.

Acetoxyacrylonitrile was prepared by the method of Sorm^{67a}. A solution of levopimaric acid (2.5 g), acetoxyacrylonitrile (5 g) and hydroquinone (0.15 g) in toluene (15 ml) was refluxed for 8 hours and then allowed to stand overnight at room temperature. Ether (100 ml) was added and the solution was washed repeatedly with water to remove the hydroquinone. The hydroquinone-free organic layer was extracted with dilute sodium hydroxide (5%, 3 x 50 ml), washed with water (3 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to give nonacidic material (0.44 g, 14%). The infrared spectrum (CHCl_3) of the nonacidic material showed bands at 1800 (s), 1750 (s), 1370 cm^{-1} (m).

The alkaline extract and the washings were combined, acidified with conc. HCl and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to give the acidic product (2.68 g, 86%) as a white foam.

In another experiment 1.5 g of levopimaric acid and 3 g of acetoxyacrylonitrile gave 0.8 g of nonacidic product and 1 g of acidic product.

The acidic products (3.78 g) from the two experiments were combined and crystallized from acetonitrile to give 1.25 g (30%) of

adduct 80a. Recrystallization from the same solvent provided the analytical sample, m.p. 195-196°. Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.30%. Found: C, 76.58; H, 8.92%. Infrared spectrum: $\nu_{\max}^{CHCl_3}$ 3200-2400 (broad), 1715-1700 (s, broad), 1410 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.25 (3H), 8.97 (6H, d., $J \approx 6.5$ c.p.s.), 8.83 (3H), 4.72 (1H), -1.3 (1H, broad). R. D. in methanol (c 0.038) positive Cotton effect curve: $[\alpha]_{700}^D 0^\circ$, $[\alpha]_{500}^D +210^\circ$, $[\alpha]_{400}^D +525^\circ$, $[\alpha]_{319}^D +7350^\circ$ (peak), $[\alpha]_{275}^D -7900^\circ$ (trough).

Esterification of adduct 80a with ethereal diazomethane gave the methyl ester 80b, m.p. 83-84°. Infrared spectrum: $\nu_{\max}^{CHCl_3}$ 1720 (s, broad), 1415 cm^{-1} (m). Mass spectrum: m/e 358 (molecular ion, 25), 316 (100).

The noncrystalline residue of the acidic product gave a further quantity of ketoacid 80a on treatment with Girard T reagent in the following manner. Noncrystalline residues from several experiments were combined. A solution of the noncrystalline material (4.7 g) and Girard T reagent (2.35 g) in ethanol (45 ml) containing acetic acid (5 ml) was refluxed on the steam bath for 2 hours. The solution was allowed to cool and then transferred to a separatory funnel containing 225 ml of ether, 225 ml of water and 10 ml of a saturated solution of sodium chloride. The contents of the separatory funnel were shaken and the aqueous layer was removed. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give non-

ketonic product (2.67 g) which was discarded. The aqueous layer was acidified with conc. HCl (11 ml) and heated on the steam bath for 45 minutes. On cooling it was extracted with ether (250 ml). The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (1.68 g) which on crystallization from acetonitrile afforded 1.1 g of ketoacid 80a.

The nonacidic product (0.44 g), obtained from the reaction of levopimaric acid with acetoxycrylonitrile was refluxed in 30 ml of 10% methanolic sodium hydroxide for 3 hours. The solution was concentrated under reduced pressure, diluted with water, acidified with conc. HCl and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (ca. 350 mg). This on crystallization from acetonitrile provided 0.2 g of ketoacid 80a.

b) Reduction of ketoacid 80a with sodium borohydride.

Sodium borohydride (55 mg) was added to a solution of ketoacid 80a (110 mg) in 20 ml of dimethoxyethane and the resulting solution was stirred for 5 hours. Fresh sodium borohydride (55 mg) was then added and stirring continued for 15 hours. The solution was then concentrated under reduced pressure, diluted with water and acidified with conc. H_3PO_4 . The product was extracted with ether, the ether solution washed with water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (105 mg) consisting of a mixture of

hydroxy acids. This was esterified with ethereal diazomethane. To the esterified material was added acetic anhydride (1.0 ml) and pyridine (0.5 ml) and the solution was allowed to stand at room temperature for 20 hours. Codistillation with toluene followed by drying in vacuo removed excess acetic anhydride and pyridine to give a mixture of acetates. The ratio of exo to endo acetate (81b : 76b) was found to be 4 : 3 from the relative intensities of the signals at τ 7.94 and τ 8.08 in the n.m.r. spectrum.

c) Reduction of ketoacid 80a with $\text{Li}/\text{NH}_3/\text{MeOH}$.

A solution of ketoacid 80a (1.0 g, 2.9 mmoles) in ether (25 ml) was added to liquid ammonia (100 ml) containing 15 ml of anhydrous methanol. Lithium metal (1.5 g) was then added in small portions with stirring over a period of 70 minutes. More methanol (5 ml) was added and stirring continued for another 40 minutes. Lithium methylete was then neutralized with ammonium chloride (15 g) and the ammonia was allowed to evaporate overnight. The residue was diluted with water (70-80 ml), acidified with conc. H_3PO_4 and extracted with chloroform (3 x 100 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to afford a mixture of hydroxy acids (1.03 g) as a white foam. Esterification with ethereal diazomethane gave a mixture of the alcohols 76a and 81a. A small portion of the mixture of alcohols was acetylated ($\text{Ac}_2\text{O}/\text{py}$), and the n.m.r. spectrum of the product

determined. The relative intensities of the signals at τ 7.94 and τ 8.08 indicated that the exo and the endo alcohols were present in the ratio of 3 : 4.

d) Isolation of the acetates 76b and 81b by chromatography on alumina.

The mixture of alcohols 76a and 81a was acetylated with acetic anhydride and pyridine in the usual manner and the product (1.1 g) was subjected to chromatography on alumina (55 g). Elution with Skellysolve B (400 ml) gave 25 mg of an unidentified material. Elution with Skellysolve B-benzene (1:1, 1.2 l) gave the oily exo acetate 81b (0.355 g, 32%). Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1640 (w), 1370 (m), 1153 (m), 1140 (m), 1025 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.37 (3H), 9.02 (6H, d., $J \approx 6$ c.p.s.), 8.86 (3H), 7.94 (3H), 6.36 (3H), 5.84 (1H, d. of d., $J \approx 9$ and 3 c.p.s.), 4.72 (1H). Continued elution with Skellysolve B-benzene (1:1, 200 ml) and benzene (100 ml) gave a mixture of exo and endo acetate (24 mg). Elution with benzene (1.3 l) gave the oily endo acetate 76b (0.475 g, 43%). Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1640 (w), 1370 (m), 1163 (m), 1140 (m), 1015 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.37 (3H), 8.98 (6H, d., $J \approx 7$ c.p.s.), 8.86 (3H), 8.08 (3H), 6.38 (3H), 5.44 (1H, d. of d., $J \approx 8$ and 3 c.p.s.), 4.72 (1H). Elution with chloroform (300 ml) gave 85 mg of an unidentified material.

e) Preparation of tosylate 76c from acetate 76b.

Acetate 76b (0.30 g) was refluxed in 10% methanolic potassium

hydroxide (30 ml) for 3 hours. The solution was concentrated on the rotary evaporator, the residue diluted with water (60 ml) and acidified with conc. HCl. The product was extracted with chloroform (3 x 50 ml), the chloroform solution washed with water, dried over anhydrous magnesium sulfate and evaporated to give the crude endo alcohol 76a (0.253 g). The infrared spectrum showed absorption at 3200-2400 cm^{-1} (w, broad). Treatment with ethereal diazomethane, followed by crystallization from Skellysolve B afforded alcohol 76a. The analytical sample, m.p. 92-93 $^{\circ}$, was obtained by recrystallization from the same solvent. Calc. for $\text{C}_{23}\text{H}_{36}\text{O}_3$: C, 76.62; H, 10.06%. Found: C, 76.77; H, 9.91%. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3570 cm^{-1} (m, broad), 1720 (s), 1635 (w), 1145 (m), 1080 (m), 1010 (m), 865 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ 9.38 (3H), 8.97 (6H, d., $J \approx 6.5$ c.p.s.), 8.86 (3H), 6.64 (1H, d. of d., $J \approx 8$ and 3 c.p.s.), 6.38 (3H), 4.75 (1H).

A solution of endo alcohol 76a (0.234 g, 0.65 mmoles) and p-toluenesulfonyl chloride (0.185 g, 0.975 mmoles) in dry pyridine (2 ml, dried over molecular sieves) was allowed to stand in the dark at room temperature for 88 hours. Water (50 ml) was then added and the organic precipitate extracted with ether (100 ml). The ether solution was washed successively with dilute H_2SO_4 (1N, 2 x 30 ml), water (30 ml), saturated solution of NaHCO_3 (2 x 30 ml) and water (50 ml). It was then dried over anhydrous magnesium sulfate, filtered and evaporated

to give tosylate 76c (0.32 g, 0.64 mmoles) as a greenish white foam.

Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1600 (m), 1350 (s), 1175 (s), 910 (s), 890 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ = 9.42 (3H), 9.02 (6H, d., $J \approx 7$ c.p.s.), 8.88 (3H), 7.60 (3H), 6.38 (3H), 5.66 (1H, d. of d., $J \approx 8$ and 2.5 c.p.s.), 4.78 (1H), 2.73 (1H, d., $J \approx 8$ c.p.s.), 2.33 (1H, d., $J \approx 8$ c.p.s.). Crystallization of tosylate 76c using a variety of solvents was not successful.

PREPARATION AND REACTIONS OF THE DIENE 82a.

a) Preparation of diene 82a.

A benzene solution of tosylate 76c (0.240 g, 0.47 mmoles) was adsorbed on a column of silica gel (6 g, BDH). The top portion of the column turned deep purple after introduction of the solution of tosylate 76c. After two hours the column was eluted. Elution with benzene (200 ml) gave the oily diene 82a (0.112 g, 0.33 mmoles, 70% yield).

Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1635 (w), 1620 (w), 980 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.13 (3H), 8.78 (3H), 8.34 (3H), 8.28 (3H), 6.36 (3H), 4.15 (1H). Ultraviolet spectrum: λ_{max} 258 m μ (ϵ , 18,000). Mass spectrum: m/e 342 (molecular ion, 46), 327 (17), 107 (100).

Elution of the silica gel column with ether (150 ml) gave a brown colored foam (0.036 g) which on crystallization from Skellysolve B afforded endo alcohol 76a.

b) Hydrolysis of diene 82a with potassium tertiary butoxide-dimethyl sulfoxide (KtBD).

The reagent was prepared by adding potassium tertiary butoxide (0.61 g, 4.5 mmoles) to 9 ml of dry dimethyl sulfoxide (dried by passing through a column of molecular sieves).

Diene 82a (0.111 g., 0.32 mmoles) was heated with KtBD (6 ml) on the steam bath for $1\frac{1}{2}$ hours. The reaction mixture was diluted with water (60 ml), acidified with conc. HCl and extracted with ether (100 ml). The ether solution was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a white foam (0.108 g). This was dissolved in ether (80 ml), extracted with 5% potassium hydroxide (3 x 30 ml) and washed with water. The alkaline extract and the washings were combined, acidified with conc. HCl and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated to give acidic material (99 mg). Crystallization from acetonitrile gave round clusters of the diene acid 82b. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3200-2400 (broad), 1685 (s, shoulder at 1725), 1630 (w), 1620 cm^{-1} (w). Nuclear magnetic resonance spectrum: τ = 9.12 (3H), 8.77 (3H), 8.32 (3H), 8.28 (3H), 4.11 (1H). Mass spectrum: m/e 328 (molecular ion, 26), 313 (11), 107 (100).

Attempted recrystallization of 82b from acetonitrile resulted in the formation of an intractable material.

c) Catalytic hydrogenation of diene 82a.

An ethanolic solution (20 ml) of diene 82a (70 mg) was hydrogenated over Pd-C (35 mg, 5% Pd) at room temperature and atmospheric pressure. After an uptake (5 ml) of hydrogen during the first 20 minutes no more absorption of the gas was noticeable. After 45 minutes the hydrogenation was stopped and the solution filtered and evaporated. The partially saturated compound 83 (68 mg) was thus obtained. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715 (s), 1655 (w), 985 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.15 (6H, d., $J \approx 6$ c.p.s.), 9.02 (3H), 8.80 (3H), 6.36 (3H), 4.93 (1H). Mass spectrum: m/e 344 (molecular ion, 21), 329 (26), 301 (39), 121 (52), 91 (100).

The above partially saturated material (57 mg) was dissolved in ethanol (20 ml) and the solution hydrogenated over Adam's catalyst (26 mg) at room temperature and atmospheric pressure. After an initial uptake of 6.6 ml in the first 10 minutes no more hydrogen was absorbed. After $3\frac{1}{2}$ hours the solution was filtered and evaporated to give 57 mg of the fully saturated, oily compound 84a. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ = 9.13 (6H, broad d., $J \approx 6$ c.p.s.), 8.92 (3H), 8.79 (3H), 6.38 (3H). Mass spectrum: m/e 346 (molecular ion, 66), 303 (21), 287 (14), 218 (86), 217 (93), 121 (59), 107 (53), 95 (79), 93 (58), 91 (48), 81 (85), 55 (100).

d) Hydrolysis of compound 84a to the acid 84b.

The fully saturated compound 84a (57 mg) was subjected to treatment with KtBD as is the case of diene 82a. The hydrolysis product was separated into acidic (37 mg) and nonacidic (10 gm) fractions. Crystallization of the acidic fraction from acetonitrile afforded 84b, m.p. 128-132°. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 3200-2400 (broad), 1690 cm^{-1} (s, shoulder at 1730 cm^{-1}). Nuclear magnetic resonance spectrum: τ 9.14 (3H, d., $J \approx 6$ c.p.s.), 9.11 (3H, d., $J \approx 6$ c.p.s.), 8.88 (3H), 8.76 (3H), -0.4 (1H, broad). Mass spectrum: m/e 332 (molecular ion, 52), 315 (13), 261 (21.5), 218 (30), 123 (39.5), 121 (47.5), 107 (30), 95 (55), 81 (57), 57(90), 55 (90), 43 (100). Exact mass measurement on the peak at m/e 332: Calc. for $\text{C}_{22}\text{H}_{36}\text{O}_2$, 332.2715; Found, 332.2718.

e) Attempted oxidative cleavage of diene 82a

To a solution of diene 82a (47 mg) in 80% acetic acid (4 ml) was added 16 mg of osmium tetroxide in 1 ml of the same solvent. Immediately on addition the solution turned brown. After 45 minutes sodium metaperiodate (65 mg) in 50% acetic acid (2 ml) was introduced and the solution kept stirred for 6 hours at room temperature. After this period it was stored in the refrigerator overnight. The solution was then diluted with water (30 ml) and extracted with ether. The dark colored ether solution was washed with dilute sodium carbonate (25 ml) and then water. It was then dried over anhydrous magnesium sulfate,

filtered and evaporated to give a dark brown foam (52 mg). The infrared spectrum showed bands at 1715 (s), 1670 (w), 1630 cm^{-1} (w).

The material was found to be intractable.

f) Controlled ozonolysis of diene 82a, - Isolation of ketone 316.

The method described by Johnson⁷⁴ was adopted with minor modifications.

To a solution of diene 82a (48 mg, 0.14 mmoles) in methylene chloride (10 ml) at -70° was added 6 ml of a saturated solution (-70°) of ozone in the same solvent. On addition, the blue color of the ozone solution quickly vanished. After 30 minutes of standing at -70° the reaction mixture was allowed to warm to room temperature, the solvent removed under reduced pressure and the residue heated with water (10 ml) containing 30% hydrogen peroxide (0.8 ml) on the steam bath for 30 minutes. The product was then extracted with chloroform (30 ml). The chloroform extract was dried over anhydrous magnesium sulfate, filtered and evaporated to give the ozonolysis product (48 mg). Extraction with dilute sodium carbonate removed acidic material and left nonacidic material (37 mg) which showed absorption at 1715 cm^{-1} (s), 1670 cm^{-1} (m), 1630 cm^{-1} (w) in the infrared and at 243 $\text{m}\mu$ in the ultraviolet. The nonacidic product was chromatographed on silica gel (4 g). Early fractions eluted with benzene (160 ml) gave an unidentified material (8 mg). The fractions eluted with benzene-ether (32:1, 60 ml) and benzene-ether (9:1, 100 ml) gave 15 mg of a material rich

in ketone 316 as judged by the infrared spectrum.

In another experiment conducted in the same manner 62 mg of diene 82a afforded 17 mg of material rich in ketone 316.

The ketone 316 rich material from the two experiments was combined and subjected to chromatography on alumina (2.5 g). Fractions eluted with benzene (120 ml) and benzene-ether (19:1, 100 ml) gave 14 mg of material which crystallized from Skellysolve B to afford 7 mg of ketone 316, identical with an authentic sample in m.p., infrared spectrum and t.l.c. behaviour.

g) Complete ozonolysis of diene 82a; isolation of the ketoacid 85a.

Ozone in oxygen was passed (0.025 ml/sec) into a solution of diene 82a (152 mg) in ethyl acetate (30 ml) at -70° for 5 minutes. The solution was allowed to stand at -70° for 2 hours and then to warm to room temperature. The solvent was removed under reduced pressure and the residue heated with water (20 ml) containing 30% hydrogen peroxide (4 ml) on the steam bath for 2 hours. The product was extracted with chloroform (3 x 40 ml), the chloroform solution dried over anhydrous magnesium sulfate, filtered and evaporated to give a white foam (117 mg). Extraction of the product with dilute sodium carbonate and subsequent treatment involving acidification, extraction with ether, etc., gave 68 mg of acidic material. Two crystallizations from ether afforded 11 mg of the ketoacid 85a, m.p. $180-193^{\circ}$.

Infrared spectrum: $\nu_{\max}^{\text{CHCl}_3}$ 3200-2400 (broad), 1730-1700 (s, broad),

1405 cm^{-1} (w). Esterification of a small sample with ethereal diazomethane afforded the methyl ester 85b. The mass spectrum on the methyl ester 85b gave a molecular ion at m/e 350.

h) Preparation of diene 82a by acetolysis of tosylate 76c.

A solution of tosylate 76c (166 mg, 0.32 mmoles) in glacial acetic acid (15 ml) containing sodium acetate (123 mg, 1.5 mmoles) was heated to reflux on a sand bath for 5 hours and then allowed to stand at room temperature overnight. Ether (100 ml) was added and the solution washed successively with water (100 ml), 10% sodium carbonate (50 ml) and water. The ether solution was dried over anhydrous magnesium sulfate, filtered and evaporated to give an oil (125 mg). The oil was subjected to chromatography on alumina (6.25 g). Elution with Skellysolve B (180 ml) and Skellysolve B-benzene (9:1, 270 ml) afforded 47 mg (0.14 mmole, 38%) of diene 82a. Continued elution with Skellysolve B-benzene (3:1, 180 ml), Skellysolve B-benzene (1:1, 90 ml) and benzene (90 ml) afforded an unidentified material (14 mg). Elution with benzene (135 ml) gave an oil (16 mg, 13%) which was found to be identical with the endo acetate 76b in t.l.c. behaviour and infrared spectrum. Further elution with more polar solvents including ether, chloroform and chloroform-methanol (19:1) afforded 25 mg of an intractable material.

ATTEMPTED TOSYLATION OF THE EXO ALCOHOL 81A.

Exo acetate 81b (650 mg) was refluxed in 10% methanolic potassium

hydroxide (30 ml) for $3\frac{1}{2}$ hours. The solution was then concentrated under reduced pressure, diluted with water (60 ml), acidified with conc. HCl and extracted with chloroform (3 x 60 ml). The chloroform solution was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to afford exo alcohol 81a (578 mg). The infrared spectrum (CHCl_3) showed a sharp band at 3590 cm^{-1} .

A solution of exo alcohol 81a (234 mg) and p-toluenesulfonyl chloride (185 mg) in dry pyridine (2 ml) was allowed to stand at room temperature for 65 hours. Following the procedure described in the case of endo alcohol 76a there was obtained 212 mg of a greenish yellow wax which slowly turned purple in color. The infrared spectrum (CHCl_3) of this product showed absorption at 1715 cm^{-1} (s), 1780 (m,

lactone). Chromatography on silica gel was ineffective in separation of the ester and the lactone. The material (142 mg) recovered from chromatography on silica gel was dissolved in benzene and filtered through a short column of alumina. Elution with benzene (100 ml) gave the ester 89 (106 mg) as an oil. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 1715 (s), 1630 cm^{-1} (w). Nuclear magnetic resonance spectrum: $\tau = 9.15$ (3H), 8.98 (3H, d., $J \approx 7$ c.p.s.), 8.97 (3H, d., $J \approx 7$ c.p.s.), 8.83 (3H), 6.36 (3H), 4.22 (1H, br. s.). Simultaneous irradiation 488 c.p.s. upfield from CHCl_3 caused the doublets at $\tau 8.98$ and $\tau 8.97$ to collapse to a broad singlet and the broad singlet at $\tau 4.22$ to sharpen to a doublet ($J \approx 2$ c.p.s.). Simultaneous irradiation 488 and 505 c.p.s. upfield from

CHCl_3 caused the broad signal at τ 4.22 to collapse to a sharp singlet.

Mass spectrum: m/e 342 (molecular ion).

An ethanolic solution (50 ml) of ester 89 (50 mg) was hydrogenated over Adams' catalyst (15 mg) at room temperature and atmospheric pressure for 45 minutes. The solution was filtered and evaporated to give an oily substance (53 mg). Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ = 9.10 (broad absorption 6H), 9.06 (3H), 8.87 (3H), 6.38 (3H).

The alumina used in the filtration of ester-lactone mixture was shaken with CH_2Cl_2 - CH_3COOH (16:1, 2 x 50 ml). The solution was filtered and evaporated to dryness. The infrared spectrum of the residue showed strong absorption at 1595 cm^{-1} ($-\text{COO}^-$). Treatment with dilute HCl gave the corresponding carboxylic acid. This was esterified with ethereal diazomethane. The esterified material showed the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715 cm^{-1} . Nuclear magnetic resonance spectrum: τ = 9.36, 9.17, 9.09, 8.93, 8.83, 8.74, 6.36, 4.75, 4.25.

4. GENESIS OF THE DEAMINATION PRODUCTS

Acetolysis of the p-toluenesulfonate 76c gave diene 82a and acetate 76b as the major products, the formation of which can be easily explained. In contrast, several products are obtained from the nitrous acid deamination of amine 29 and their genesis is not immediately obvious. On the basis of the carbon skeleton the products of deamination can be divided into two groups. Acetate 402 (52), ketoacetate 376 (55a) and nitroacetate 400 (57) possess a bicyclo[2.2.2]octane system. Ketone 316 (59), the trinitro compound 60, the dinitro compound 61 and the nitroalcohol 73 have a bicyclo[3.2.1]octane system incorporated in their structures. Except for ketone 316 the compounds of the latter group are nitrated substances. Genesis of the compounds which possess a bicyclo[3.2.1]octane system in the skeleton will be discussed first.

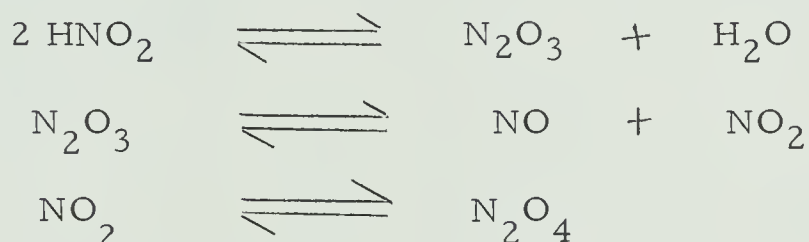
Although occasional references to isolation of minor amounts of nitrated products from nitrous acid deamination are found in the literature a detailed investigation of these products is seldom reported. Apparently these are derived by nucleophilic attack of a nitrite ion on the carbonium ion produced by reaction of nitrous acid with the amine. The formation of the trinitro compound, the dinitro compound and the nitroalcohol, however, cannot be explained in terms of a nucleophilic attack of nitrite ion on carbonium ion(s) derivable from amine 29. In view of the fact that a carbonium ion derived from tosylate 76c leads

mainly to the formation of diene 82a which possesses a rearranged skeleton it seems reasonable to speculate that the carbonium ion produced from amine 29 also forms the diene 82a as the major initial product. Subsequent reactions of diene 82a with nitrating species originating from the nitrous acid could then give rise to the nitro compounds possessing the rearranged skeleton.

In order to test the validity of this hypothesis an acetic acid solution of diene 82a was treated with sodium nitrite as in the case of amine 29. The infrared spectrum of the crude product thus obtained showed absorption in the region $1540\text{-}1560\text{ cm}^{-1}$ indicative of the presence of nitrated products. Crystallization of the product afforded the trinitro compound in ca. 13% yield. Attempts to isolate other compounds from the noncrystalline residue by chromatography were unsuccessful. In view of the fact that diene 82a reacts with nitrous acid (or nitrogen oxides derived from it) to give a nitrated product, it was of interest to see if use of a limited amount of sodium nitrite in the deamination of amine 29 would lead to the diene 82a. Accordingly the deamination of 29 in aqueous acetic acid was carried out using one equivalent of sodium nitrite. A nonbasic product was isolated in ca. 16% yield. Crystallization of this product from ether afforded the trinitro compound (ca. 4%) and a noncrystalline residue. Chromatography of the latter on alumina gave the dinitro compound (ca. 7%) and a material (ca. 9%) rich in nitroalcohol as judged by the

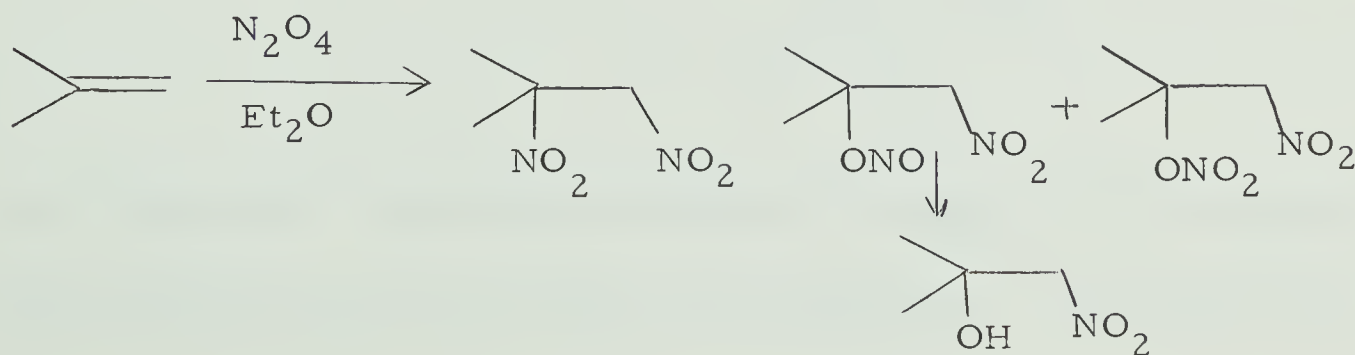
infrared spectrum. Diene 82a could not be isolated. It thus seems that deamination effected by using limited amounts of sodium nitrite results in a lower yield of the nonbasic product but does not otherwise affect the course of the reaction.

Nitrous acid as such is not known to be involved in addition reactions of olefins. It can however give rise to a variety of oxides of nitrogen which are reactive towards olefins. Nitrous anhydride, nitric oxide, nitrogen dioxide and dinitrogen tetroxide are known to be present under equilibrium conditions⁷⁶ as indicated below.

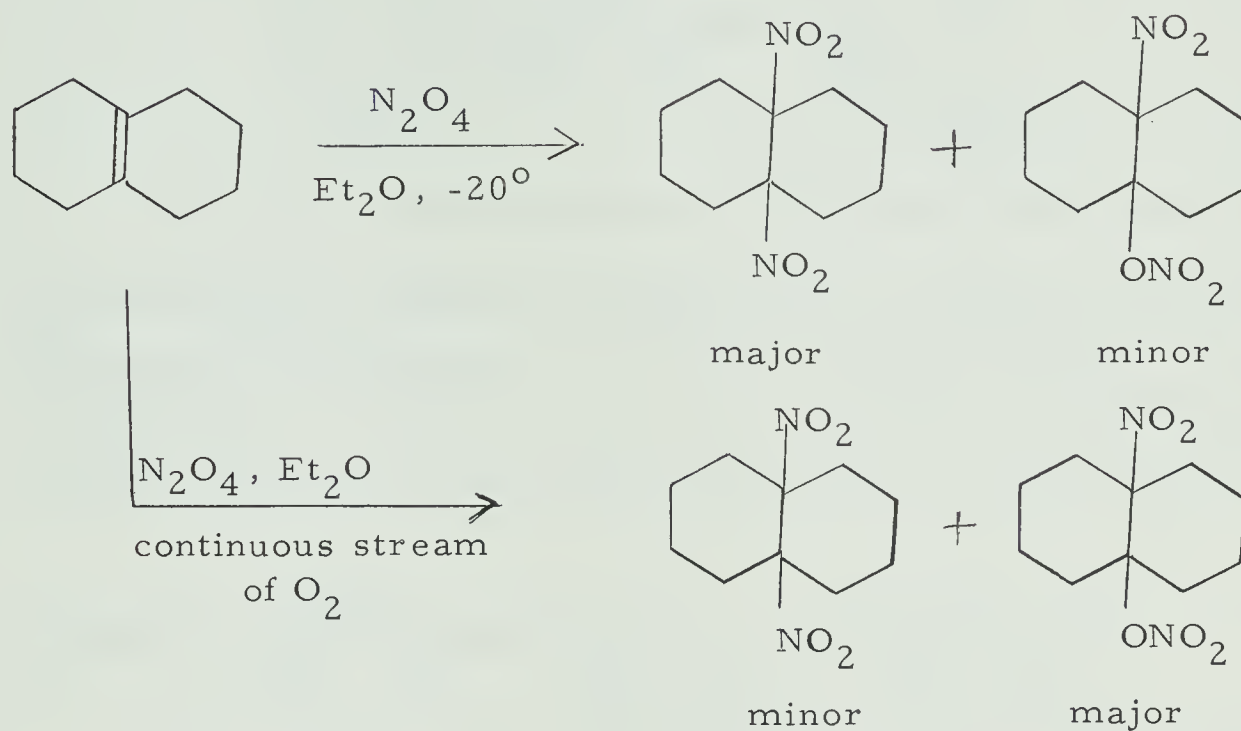


Before discussing the possible modes of reaction of these oxides with diene 82a a summary of previous investigations relevant to this subject is in order.

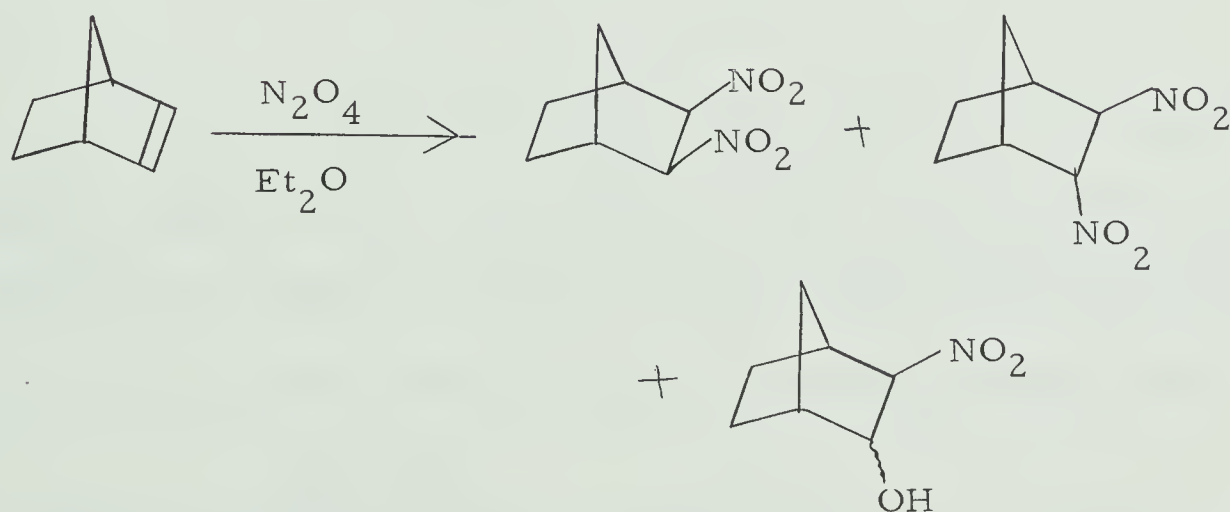
Extensive studies by Levy et al⁷⁷ have shown that reactions between olefins and dinitrogen tetroxide in solvents such as ether or an ester give rise to vicinal dinitro compounds, nitronitrites and nitronitrates as the major products. Cyclic olefins react with dinitrogen



tetroxide in an analogous fashion⁷⁸. The presence of oxygen plays an important part in determining the nature of products.

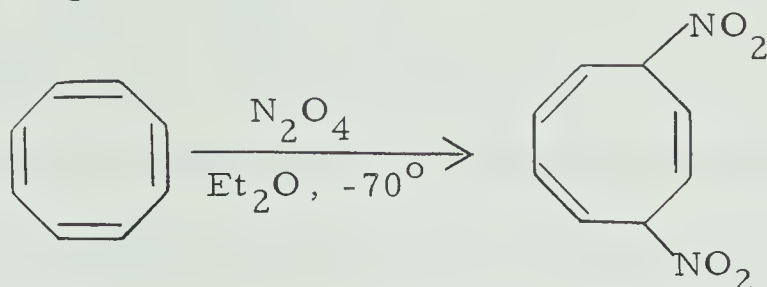


Norbornene⁷⁸ on treatment with dinitrogen tetroxide at 0° in ethyl ether gives a mixture of exo-cis-dinitro, trans-dinitro and hydroxy

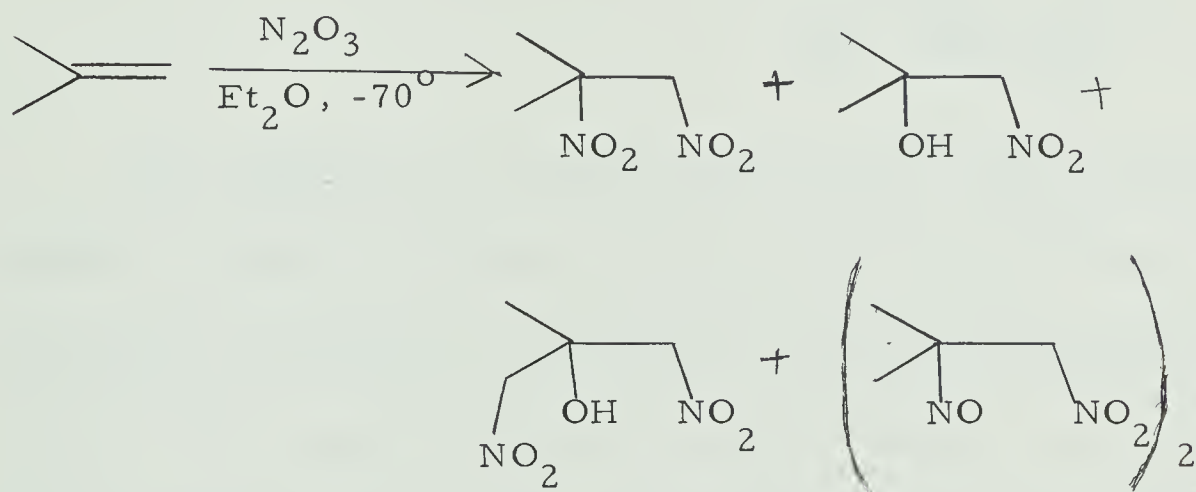


nitro compounds. Significantly products resulting from rearrangement are not obtained from the reaction with norbornene. An example of a

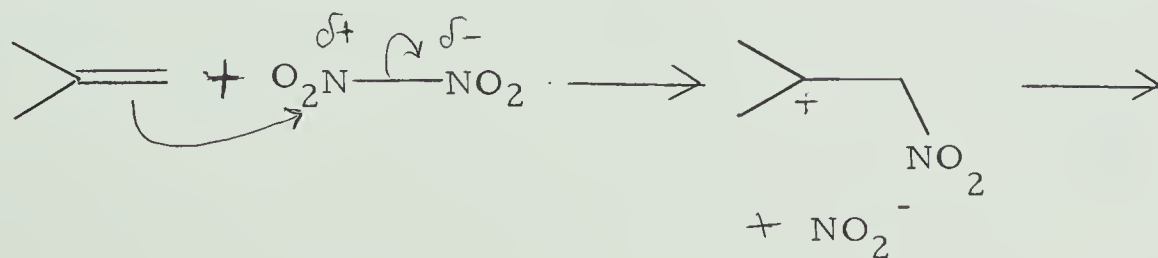
1,4 addition of nitro groups⁷⁸ is provided by the reaction of cyclooctatetraene with dinitrogen tetroxide.



Reaction⁷⁷ between nitrous anhydride and olefins provides nitro-nitroso adducts in addition to vicinal dinitro compounds and nitroalcohols derived from nitronitrites. It has been reported⁷⁷ that the presence of oxygen suppresses the formation of nitronitrosites in this reaction.

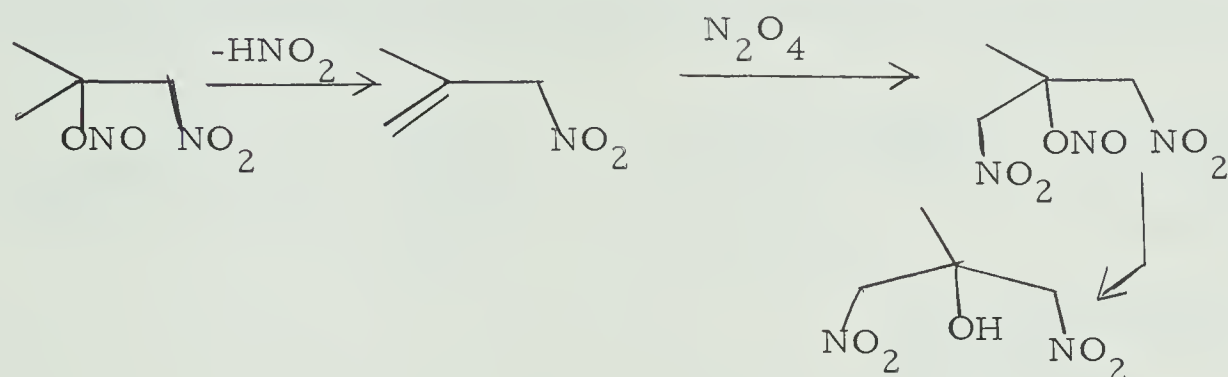


Earlier Ingold⁷⁹ had suggested that addition of dinitrogen tetroxide to olefins in ether-like solvents involves initial dissociation of dinitrogen tetroxide into nitronium (NO_2^+) and nitrite (NO_2^-) ions and subsequent reactions of these ions with the carbon-carbon double bond.

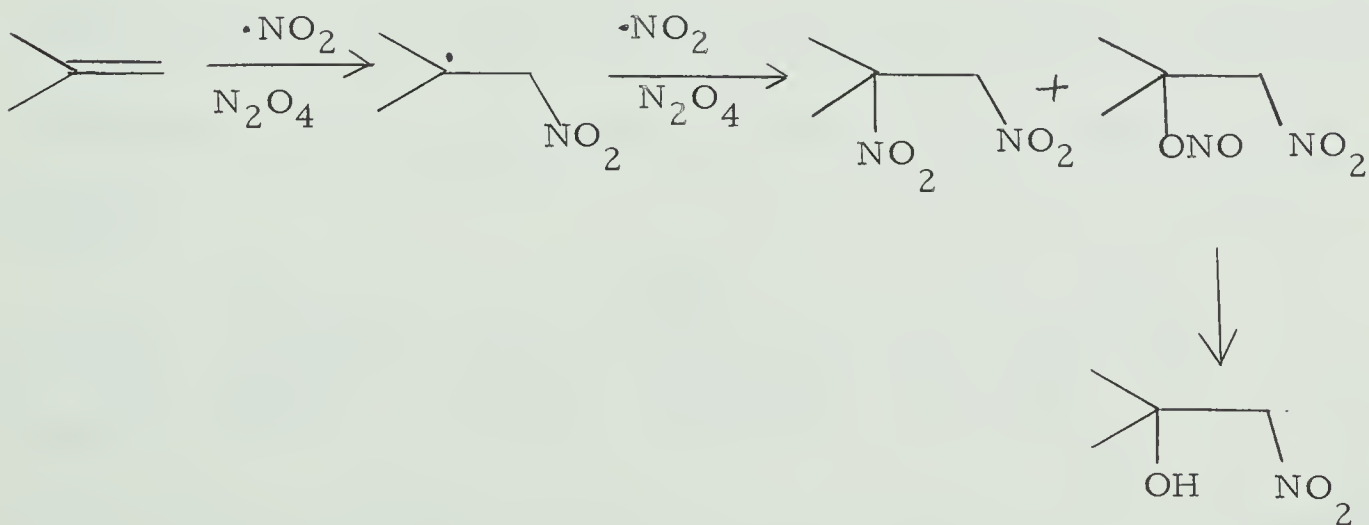




The nitronitrite presumably gives a hydroxynitro compound by hydrolysis and a hydroxydinitro compound by a process such as indicated below.

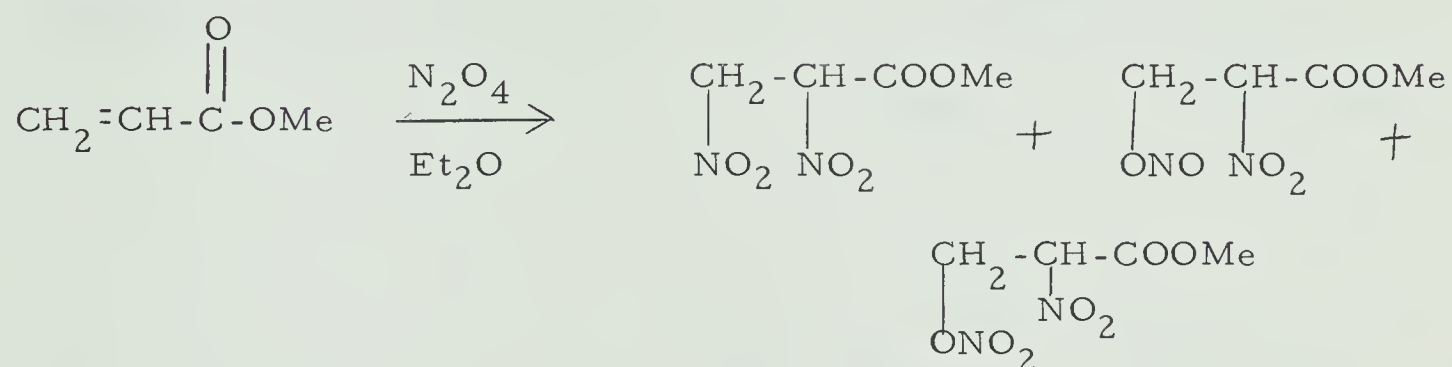


The suggestion concerning the heterolytic attack of dinitrogen tetroxide on olefins has been contradicted by Shechter⁸⁰ who proposed a homolytic mechanism for the addition of dinitrogen tetroxide to carbon-carbon double bonds in ether-like solvents. According to this mechanism the reaction is presumed to proceed as follows.

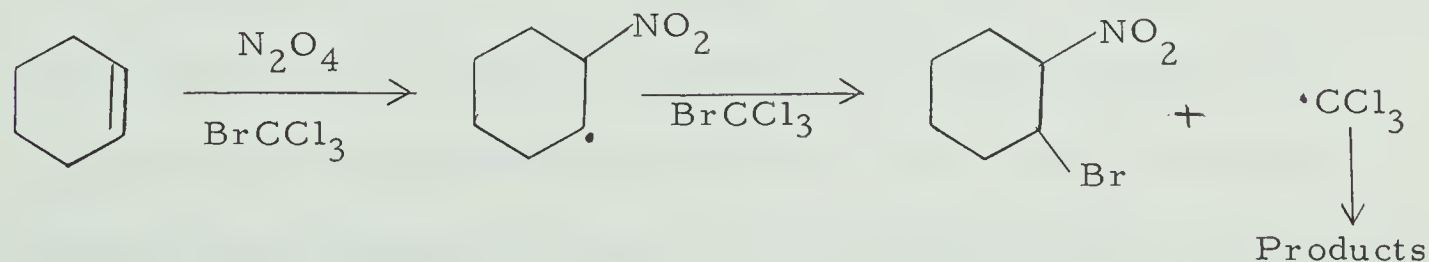


The evidence in support of the homolytic mechanism of addition is as follows⁸⁰:

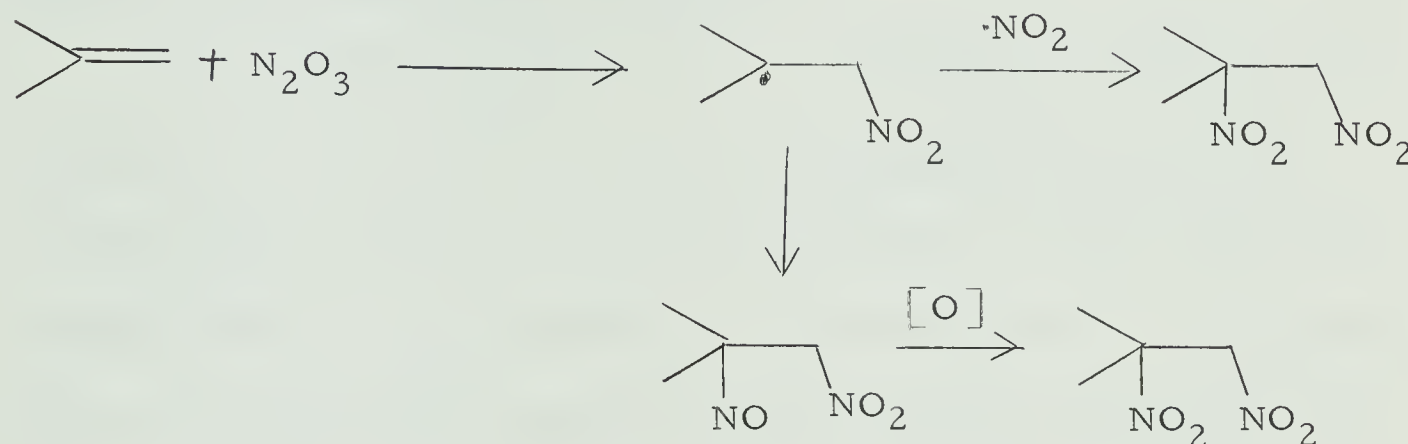
a) Weakly basic solvents such as ether form adducts with dinitrogen tetroxide. Spectroscopic examination of these adducts indicated the absence of ions NO^+ , NO_2^+ , NO_2^- or NO_3^- . b) If the mechanism suggested by Ingold is correct reaction between methyl acrylate and dinitrogen tetroxide should lead to the following products.



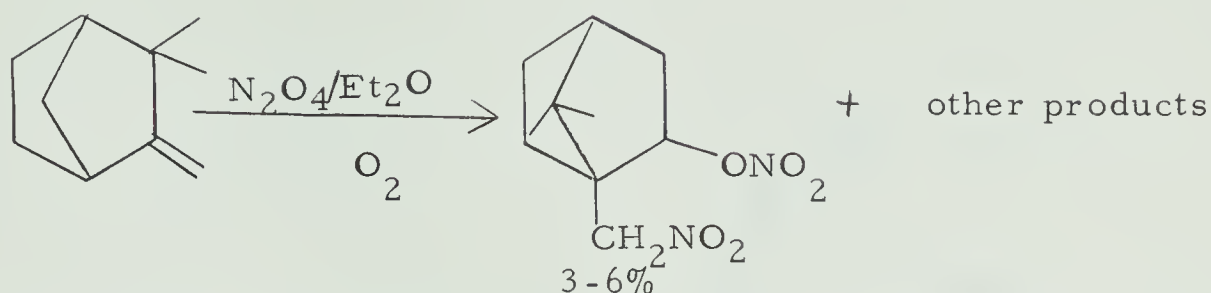
Actually the products obtained from this reaction contain a nitro group on the terminal carbon atom and the nitrite and nitrate functions on the α -carbon atom. This suggests that electrophilic attack by NO_2^+ is not involved. A homolytic addition mechanism, however, explains the formation of the products obtained. c) The homolytic nature of the reaction between dinitrogen tetroxide and olefins is further substantiated by demonstrating the participation of radical transfer agents such as BrCCl_3 .



The similarity in the nature of the products obtained from the reaction of nitrous anhydride with olefins suggests that an analogous homolytic mechanism is operative in these reactions. The formation of vicinal dinitro compounds in the reaction between nitrous anhydride and olefin is believed⁸⁰ to involve either oxidation of the nitronitroso compound or a pairing of the β nitro radical with NO_2 :



It should be borne in mind that the proposed homolytic mechanism for the addition of N_2O_4 to olefins is mainly based on the results obtained from reactions in ethereal solvents. It is possible that in solvents such as acetic acid an ionic mechanism might be operative to a significant degree. There is reason to believe that even in ethereal solvents the reaction might proceed to a certain extent by ionic mechanism with certain olefins. For example, camphene⁸¹ on treatment with dinitrogen tetroxide in ether is reported to give in low yield a nitronitrate possessing a rearranged skeleton. The formation of the nitronitrate is best explained in terms of a rearrangement of an intermediate



carbonium ion produced by an electrophilic attack of NO_2^+ on the carbon-carbon double bond of camphene.

In the light of this discussion it is possible to rationalize the formation of the nitrated compounds obtained from the deamination of amine 29 on the basis of reactions of the diene 82a with dinitrogen tetroxide and/or nitrous anhydride. It is noteworthy that a compound of the nitronitroso type, expected from the reaction of diene 82a and nitrous anhydride has not been isolated from the products of deamination. If such a compound was indeed formed it appears that it underwent further oxidation to give a product indistinguishable from that derived by reaction of dinitrogen tetroxide with diene 82a. Since complete product balance was not obtained it is also possible that such products eluded isolation. Several possibilities for the formation of the trinitro compound 60 from diene 82a by reactions with dinitrogen tetroxide may be envisioned as shown in Chart I. The dinitro compound 61 is presumably produced by elimination of nitrous acid from the trinitro compound and/or the isomeric compound 60a.

By analogy with dinitro compound 61 nitroalcohol 73 may be

CHART I

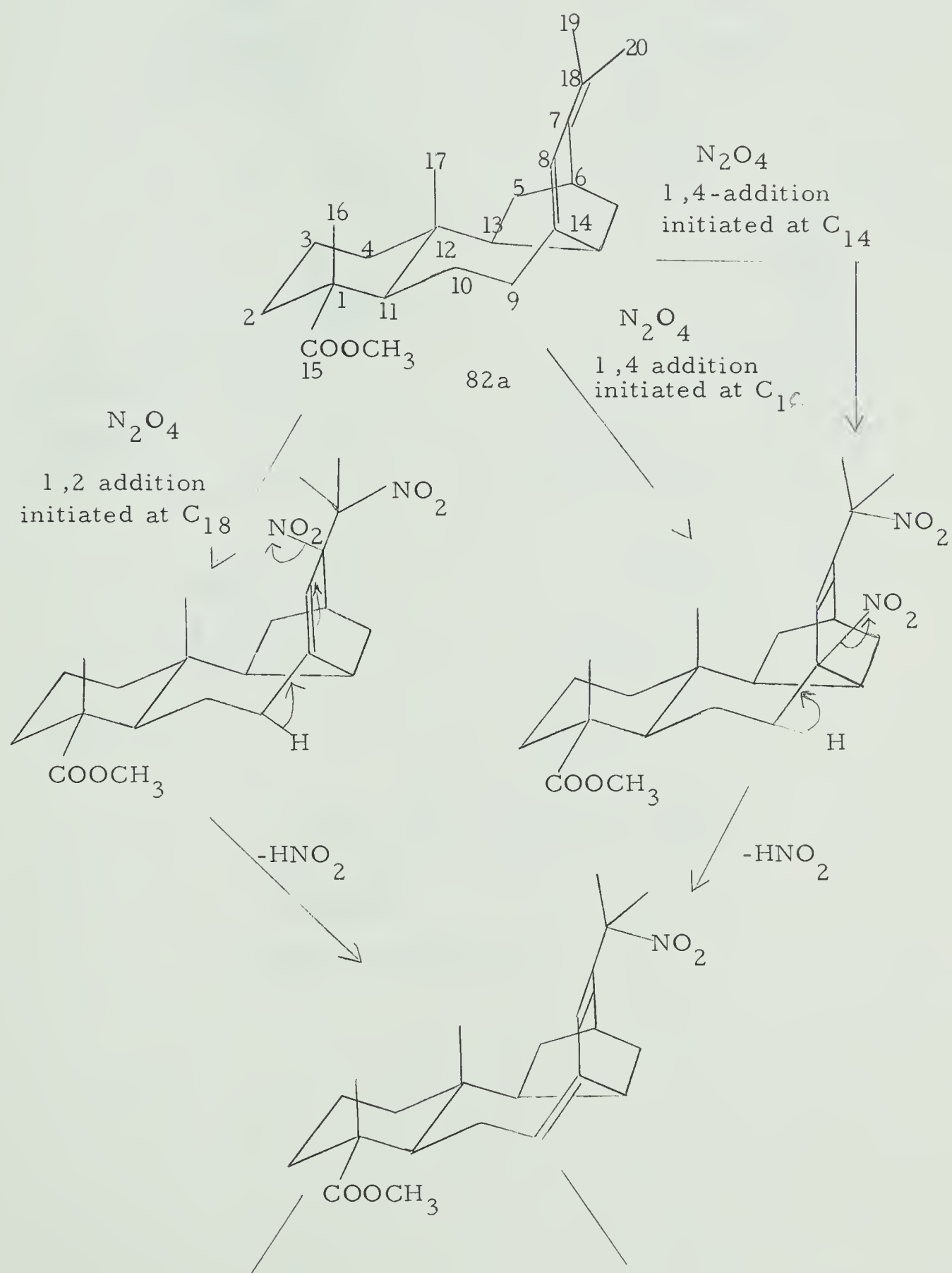


CHART I - Continued

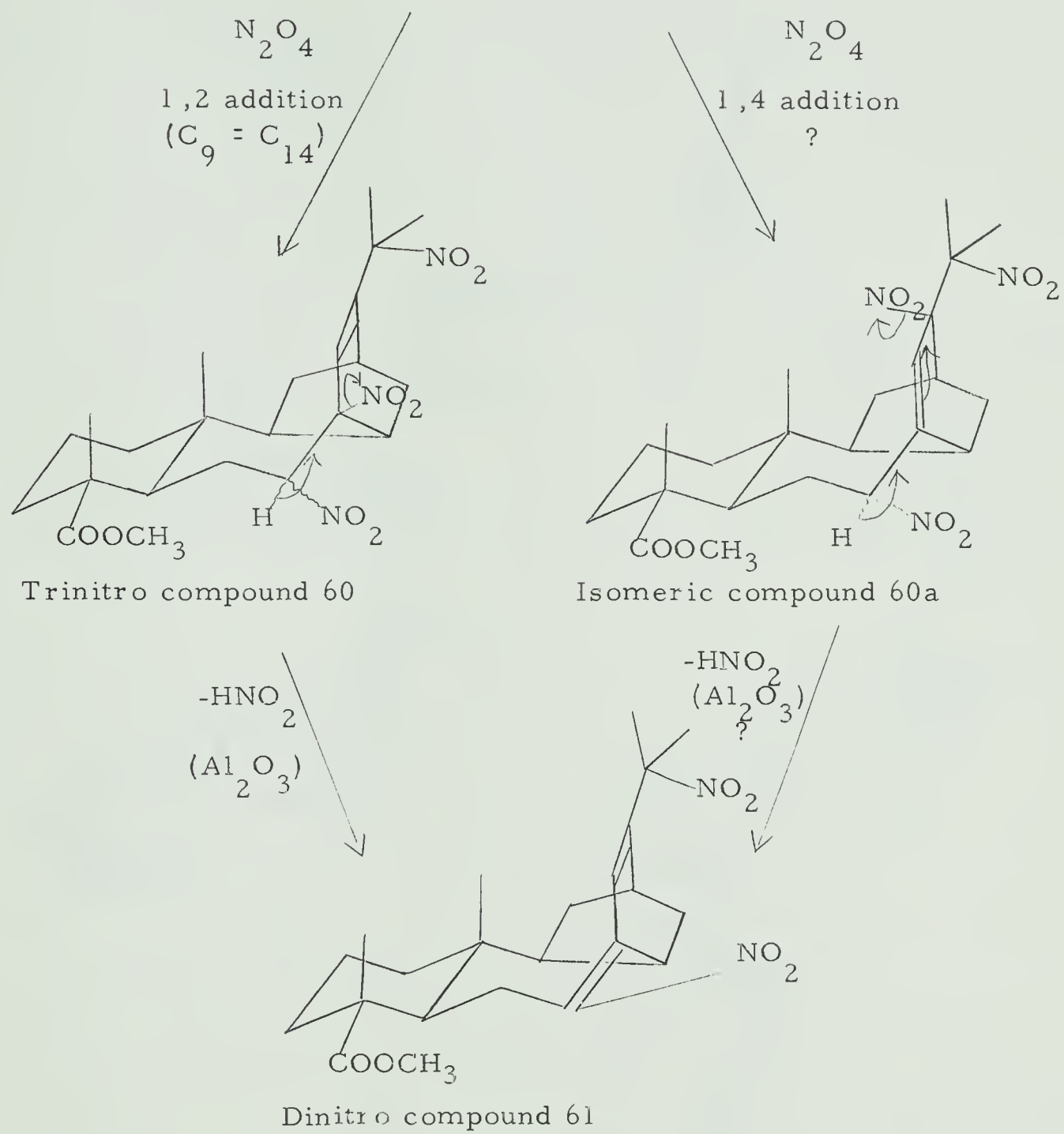


CHART II

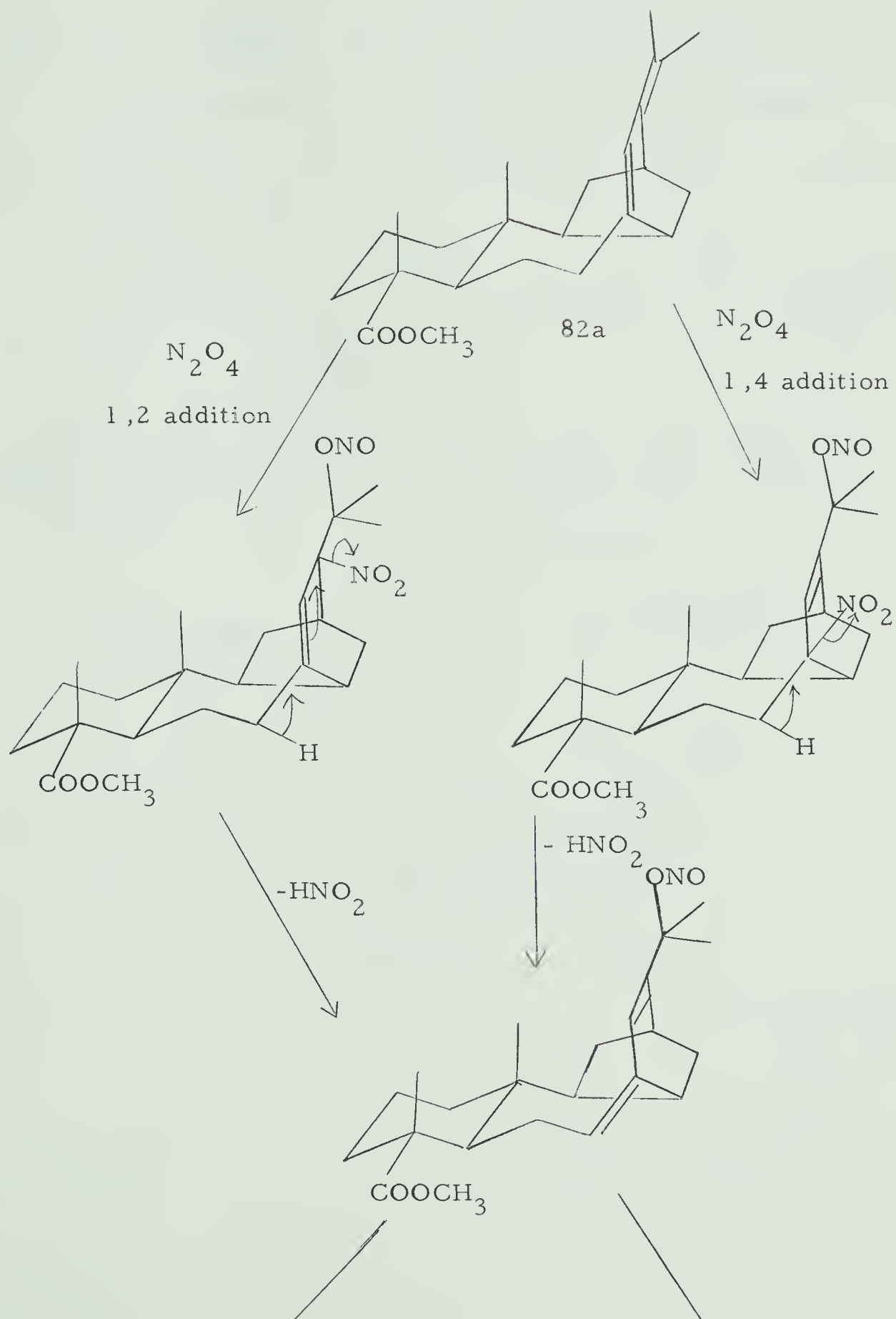
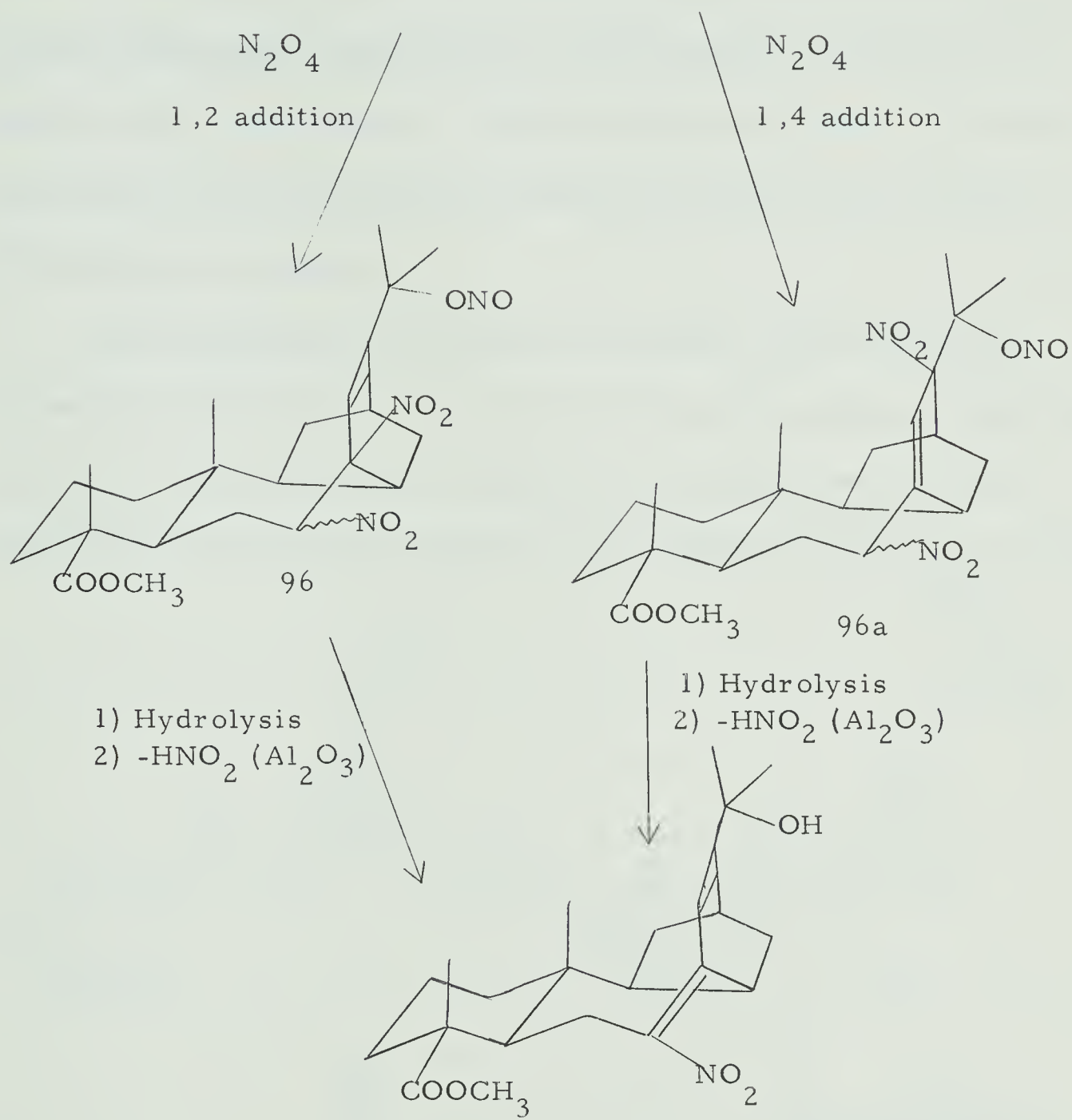
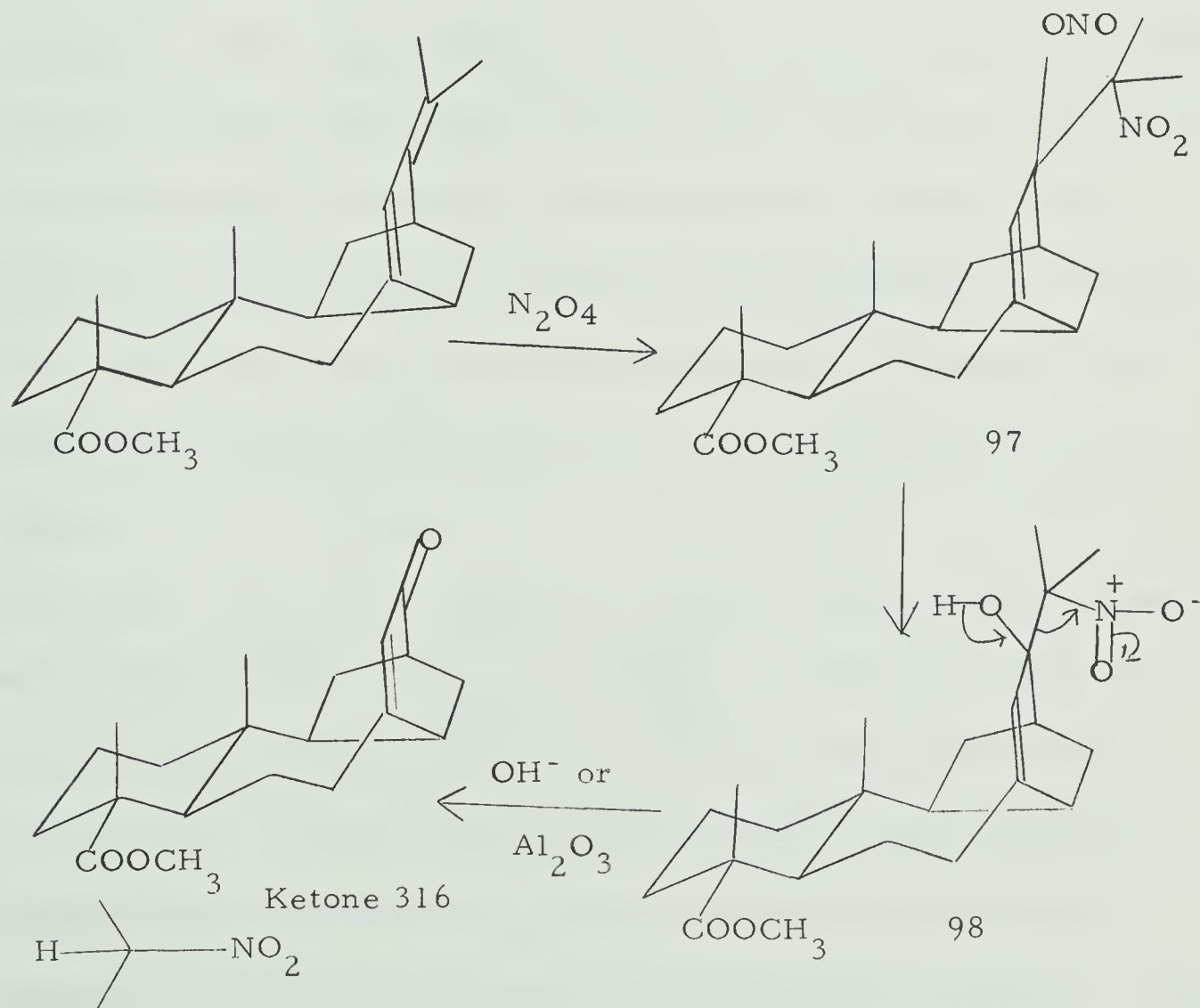


CHART II - Continued



produced by elimination of nitrous acid from precursors such as 96 and 96a (Chart II). It is reasonable to assume that the hydroxyl group in the nitroalcohol is derived from a nitrite group by hydrolysis in aqueous acetic acid medium. Chart II shows some ways in which the precursors 96 and 96a might be obtained from diene 82a by reaction with dinitrogen tetroxide.

Although ketone 316 (59) does not contain a nitro group its formation probably involves a reaction between diene 82a and dinitrogen tetroxide. Ketone 316 can be visualized as arising from the nitro-nitrite 97 which could be formed by vicinal addition of dinitrogen tetroxide



to the \triangle^{7-18} double bond of diene 82a. Hydrolysis of the nitronitrite 97 to the hydroxynitro compound 98 followed by a reverse Henry reaction either under the alkaline conditions of the work-up or during the chromatography on alumina would give ketone 316.

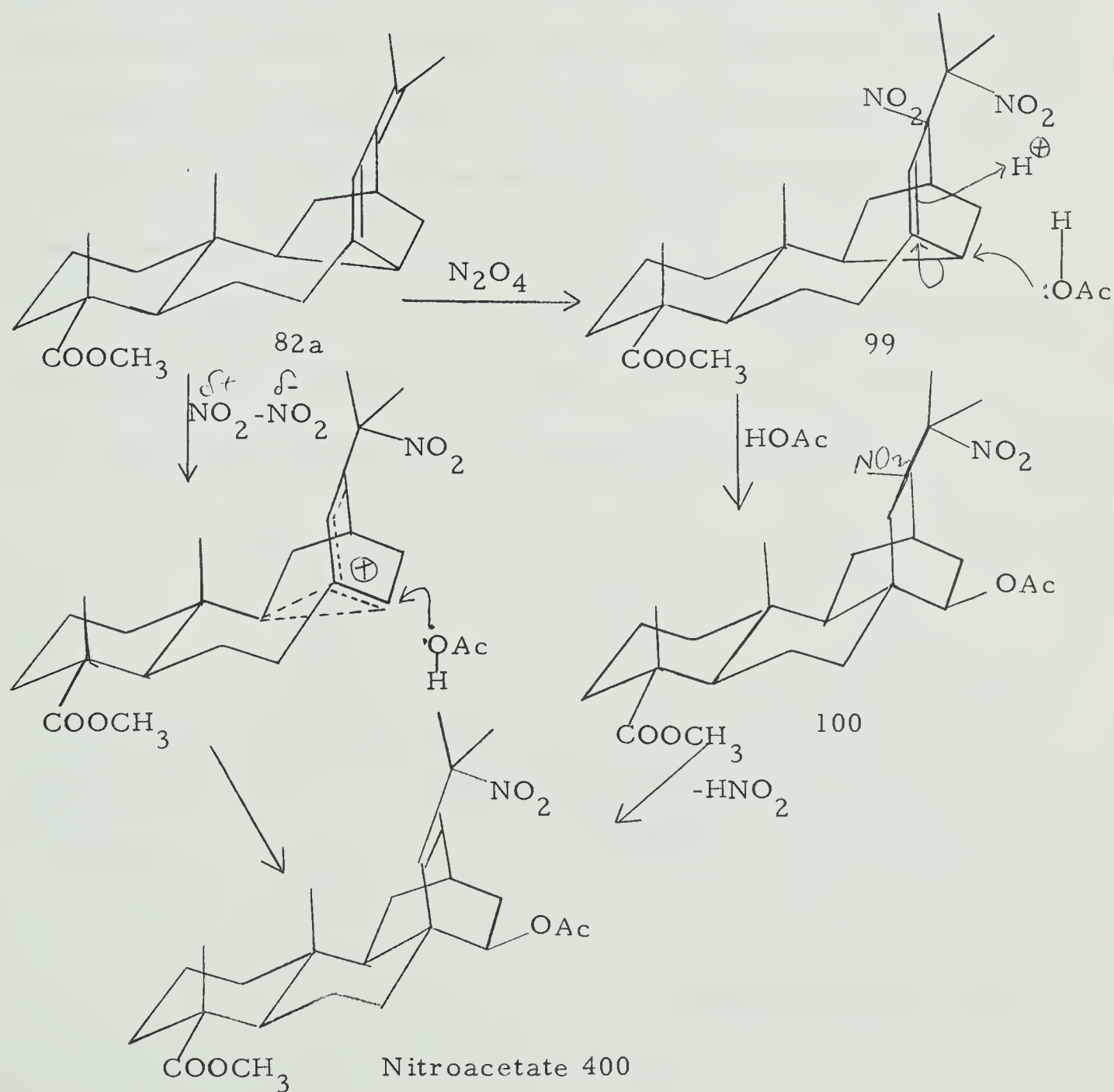
In order to test the validity of the hypothesis regarding the formation of the trinitro compound, dinitro compound and nitroalcohol the diene 82a was subjected to reaction with dinitrogen tetroxide in ether. It was of interest to see if the suggested precursors of the dinitro compound and nitroalcohol are formed in this reaction. An ether solution (0° C) of diene 82a was treated with an excess of dinitrogen tetroxide. The product obtained from this treatment gave on crystallization from ether the trinitro compound 60 in 7-8% yield. The non-crystalline material remaining was subjected to chromatography on silica gel. Early fractions from this chromatography gave a small amount ($\approx 5\%$) of material whose infrared spectrum contained bands attributable to a NO_3 and a NO_2 group. The next few fractions gave material, the infrared spectrum of which indicated the presence of a NO_2 group. The n.m.r. spectrum displayed lowfield methyl signals attributable to either $\text{C}=\text{C}\begin{matrix} \text{Me} \\ \text{Me} \end{matrix}$ or $-\text{C}\begin{matrix} \text{Me} \\ \text{Me} \\ \text{NO}_2 \end{matrix}$. The exact nature of this product remained obscure since its isolation in pure form was not accomplished. Further elution of the silica gel column afforded material which contained a NO_2 group as indicted by the infrared spectrum. This material was rechromatographed on alumina. The

infrared and ultraviolet spectra of the material eluted in the early fractions from this chromatography resembled those of the dinitro compound 61. Material from the later fractions possessed spectral properties similar to those of nitroalcohol 73. Further examination of these products was not undertaken since the amount of these materials was small.

To determine whether acetic acid as solvent would give a more tractable product, a solution of diene 82a in acetic acid was subjected to reaction with dinitrogen tetroxide. The product obtained from this reaction gave on crystallization from ether the trinitro compound 60 in ca. 24% yield. The noncrystalline material was subjected to chromatography on alumina. This provided the dinitro compound 61 in ca. 13% yield. In addition, material which presumably contained the nitroacetate 400 (57) was isolated. This material on further purification by chromatography on silica gel afforded a small amount of a crystalline substance which was found to be nitroacetate 400 (IR spectrum, t.l.c. behaviour).

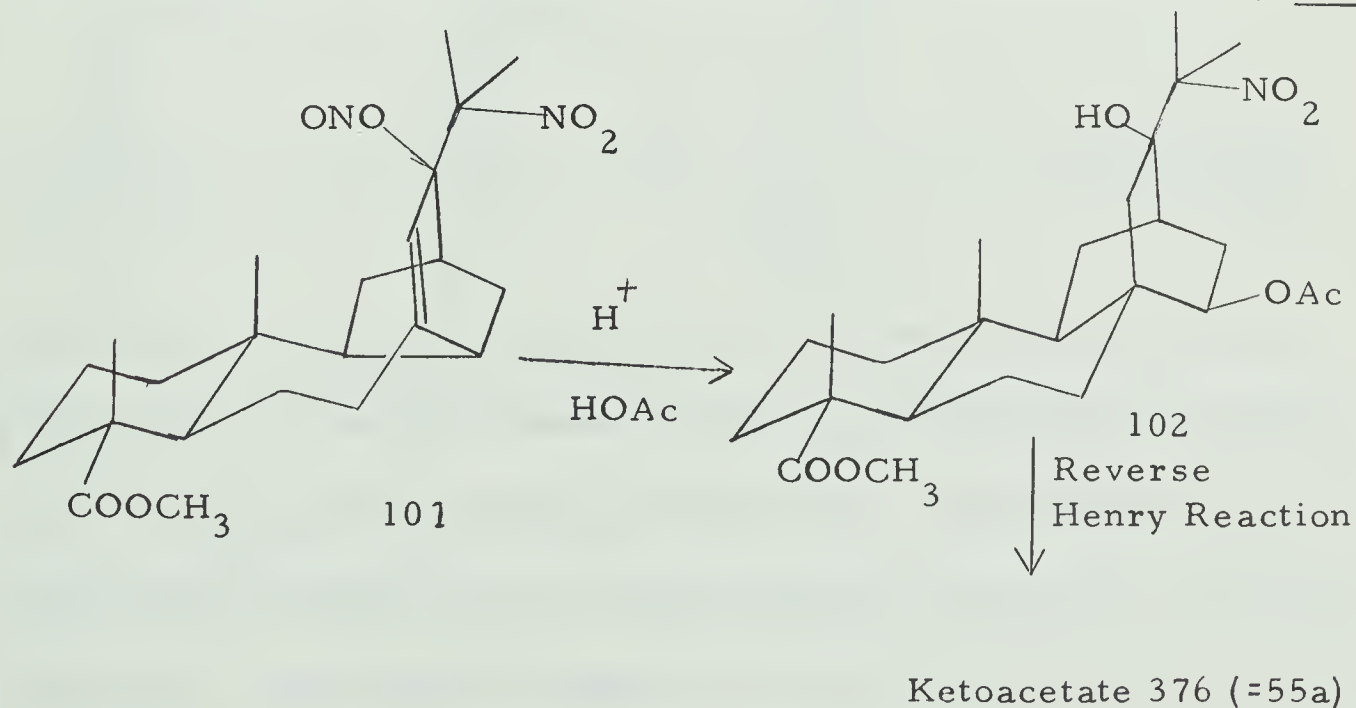
Thus the experiments undertaken for the purpose of gaining information about the nature of the intermediate(s) between the diene and the dinitro compound and nitroalcohol were not very informative. However the reaction of diene 82a with dinitrogen tetroxide in acetic acid offered a clue with regard to the genesis of the compounds possessing a bicyclo $\left[2 \cdot 2 \cdot 2\right]$ octane system.

In addition to possessing a bicyclo[2.2.2]octane moiety in their skeleton, acetate 402 (52), ketoacetate 376 (55a), and nitroacetate 400 (57) possess a C-22 acetoxyl group, probably endo-oriented. Isolation of nitroacetate 400 from the product obtained by treatment of diene 82a with dinitrogen tetroxide in acetic acid suggested that diene 82a is involved in the formation of this compound. Two possible routes leading to the formation of nitroacetate 400 are indicated below.



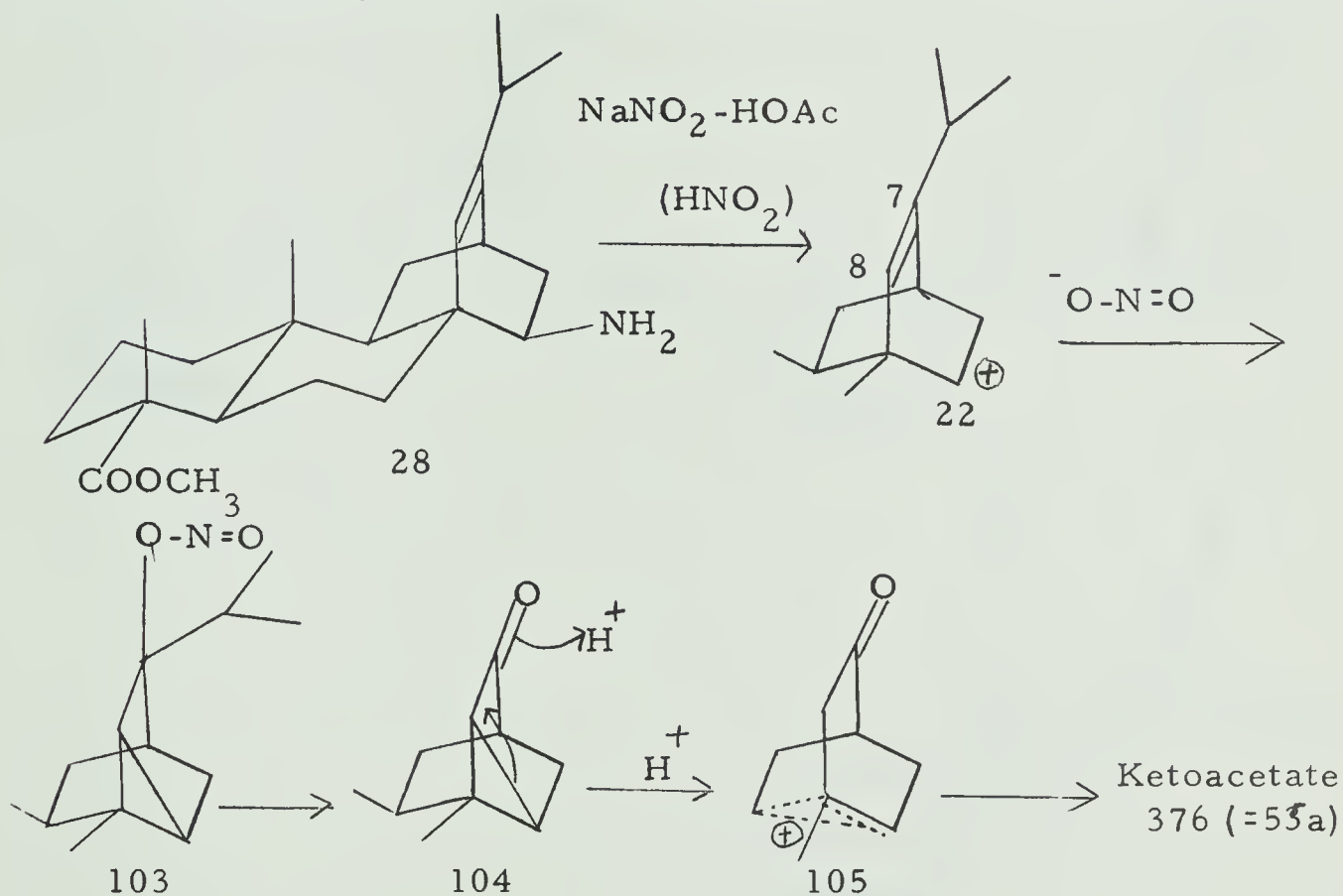
The initial step in route (1) involves vicinal addition of dinitrogen tetroxide to the \triangle^{7-18} double bond of diene 82a to produce the intermediate dinitro compound 99. In the subsequent step or steps protonation of the \triangle^{8-14} double bond, migration of the C-13,22 bond and nucleophilic attack at C-22 by acetic acid occurs to produce the intermediate 100. Loss of nitrous acid from 100 leads to the formation of nitroacetate 400. Route (2) involves an electrophilic attack by NO_2^+ at C-18 of diene 82a. The carbonium ion thus produced undergoes skeletal rearrangement and nucleophilic attack by acetic acid at C-22 to give nitroacetate 400. In aqueous acetic acid media nucleophilic attack by either acetic acid or water would lead to a mixture of acetate and alcohol.

A modification of route (1) suggested for the formation of nitroacetate 400 can be utilized to rationalize the formation of ketoacetate 376. This modification involves formation of nitronitrite 101 by vicinal



addition of dinitrogen tetroxide to the \triangle^{7-18} double bond of diene 82a. A sequence similar to that suggested in route (1), and hydrolysis of the nitrite function then leads to the formation of 102. Compound 102 could undergo a reverse Henry reaction to give ketoacetate 376 in a manner analogous to that suggested earlier for the formation of ketone 316.

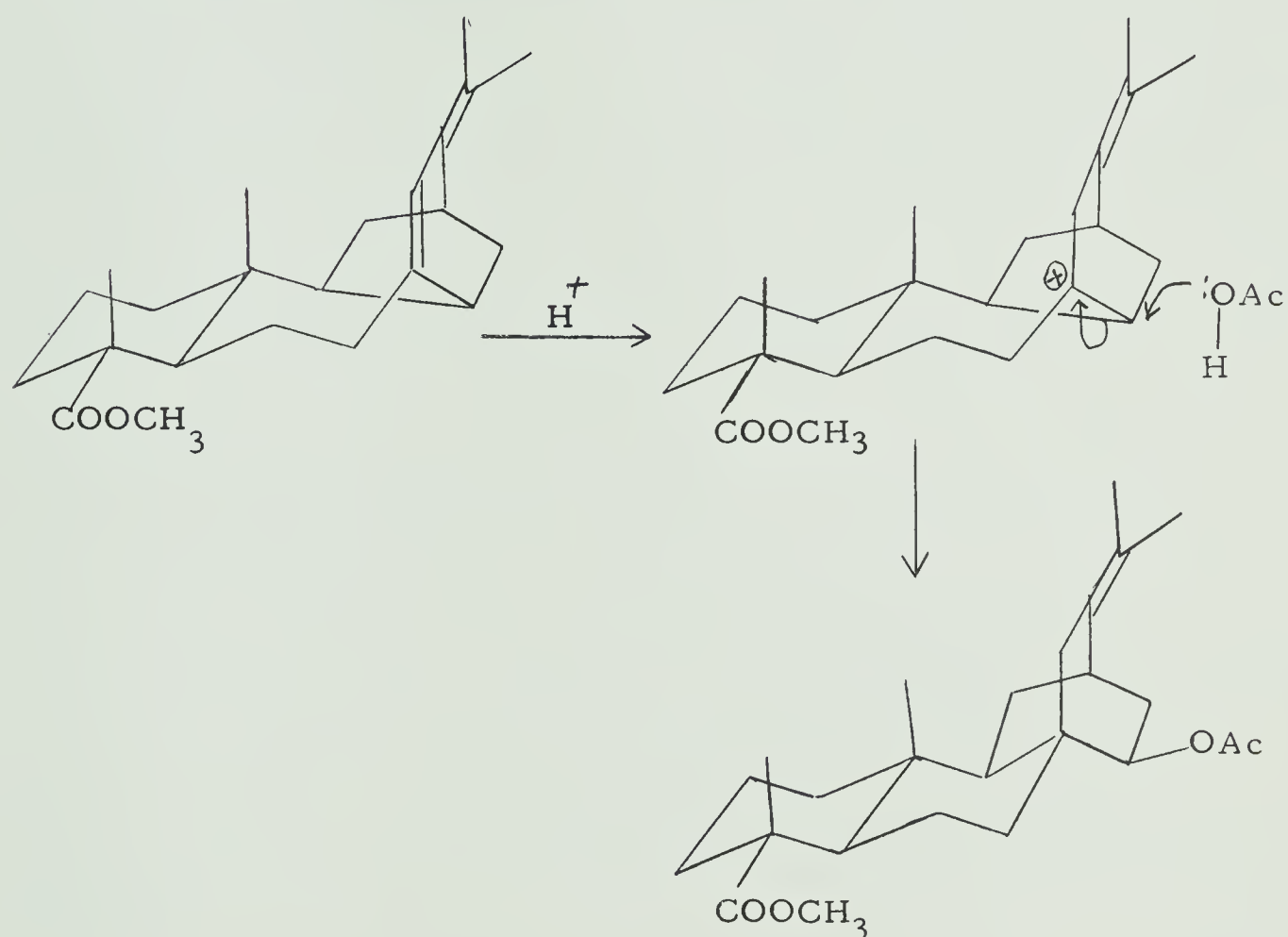
Alternatively, ketoacetate 376 could be formed from amine 29 via the cyclopropyl ketone 104 as indicated in the following scheme.



This scheme involves formation of a carbonium ion from amine 29, participation of the \triangle^{7-8} double bond and nucleophilic attack by NO_2^- at C-7 to produce the cyclopropyl nitrite 103. Homolytic cleavage of the O-N bond in the nitrite function could give rise to the cyclopropyl ketone 104. Nucleophilic attack by acetate ion at C-22 in the carbonium ion 105, generated by protonation of the ketone 104 would lead to keto-

acetate 376.

Genesis of acetate 402 is the most difficult to rationalize. By analogy with the related compounds nitroacetate 400 and ketoacetate 376, acetate 402 may be derived from diene 82a. If the latter substance is indeed the precursor of acetate 402 a scheme such as shown below could explain the formation of this compound.



This scheme involves selective protonation at C-8, which is rather difficult to explain since protonation at the terminal carbon of a conjugated diene should be a favored process. In order to ascertain whether protonation at C-8 of diene 82a is of importance this substance was subjected to treatment with HOAc-HClO_4 . The product obtained

from this reaction contained endo acetate 76b and acetate 402 (3:1) as evidenced by the infrared and the n.m.r. spectra. The presence of endo acetate 76b was confirmed by isolation of the endo alcohol 76a from the acetate mixture after alkaline hydrolysis.

EXPERIMENTAL

Reaction of diene 82a with nitrous acid.

To a solution of diene 82a (47 mg) in glacial acetic acid (1 ml) was added with stirring sodium nitrite (50 mg) over a period of 15 minutes. The reaction mixture was allowed to stand overnight and more sodium nitrite (50 mg) was added. After one hour of stirring the reaction mixture was diluted with water (10 ml) and basified with 10% NaOH (10 ml). The product was extracted with ether (60 ml), the ether extract washed with water, dried over anhydrous magnesium sulfate and evaporated to give a grey colored foam (54 mg). An ether solution of this foam was seeded with a crystal of trinitro compound and stored in the refrigerator overnight. The crystalline compound (7 mg, 13%) isolated from the cooled ether solution was found to be identical with the trinitro compound 60 in melting point and the infrared spectrum. The noncrystalline residue was subjected to chromatography on alumina. The material eluted from the column was intractable.

Deamination of amine 29 with limited amount of sodium nitrite.

To a solution of amine 29 (970 mg, 2.7 mmoles) in 50% aqueous acetic acid (11 ml) was added with stirring sodium nitrite (190 mg, 2.7 mmoles) in small portions over a period of one hour. The reaction mixture was stirred for another 3 hours and then subjected to a work-up

THEORY OF THE EARTH

CHAPTER I

OF THE ORIGIN OF THE EARTH

SECTION I

OF THE ORIGIN OF THE EARTH

SECTION II

OF THE ORIGIN OF THE EARTH

SECTION III

OF THE ORIGIN OF THE EARTH

SECTION IV

OF THE ORIGIN OF THE EARTH

SECTION V

OF THE ORIGIN OF THE EARTH

SECTION VI

OF THE ORIGIN OF THE EARTH

SECTION VII

OF THE ORIGIN OF THE EARTH

SECTION VIII

OF THE ORIGIN OF THE EARTH

SECTION IX

OF THE ORIGIN OF THE EARTH

SECTION X

OF THE ORIGIN OF THE EARTH

SECTION XI

OF THE ORIGIN OF THE EARTH

SECTION XII

OF THE ORIGIN OF THE EARTH

in the usual manner. An ether solution of the nonbasic product (160 mg, 16.5%) was seeded with a crystal of the trinitro compound and stored in the refrigerator overnight. Decantation of the ether solution gave crystalline trinitro compound (6 mg, 4%). The noncrystalline residue (145 mg) was subjected to chromatography on alumina (6 g). Elution with Skellysolve B (100 ml), Skellysolve B-benzene (1:1, 75 ml) and benzene (75 ml) gave an unidentified oily material (13 mg). Further elution with benzene (25 ml) and benzene-ether (32:1, 50 ml) afforded a yellowish green foam (12 mg) which crystallized from ethanol to give the dinitro compound (10 mg). Elution with benzene-ether (32:1, 50 ml) and benzene-ether (9:1, 25 ml) gave a yellowish green foam (10 mg) which contained the dinitro compound and ketone 316 as judged by the infrared spectrum. Continued elution with benzene-ether (100 ml) and ether-chloroform (1:1, 50 ml) afforded a yellow foam (14 mg). The infrared spectrum of this foam contained bands at 3590 (m), 1720 (s), 1610 (w), 1500 (m), 1320 cm^{-1} (m) attributable to nitroalcohol 73. Further elution of the alumina column with chloroform (100 ml) gave intractable material (28 mg).

Reaction of diene 82a with N_2O_4 in ether.

To an ice-cold, magnetically stirred solution of diene 82a (208 mg, 0.61 mmole) in anhydrous ether (40 ml) was added an ether solution of N_2O_4 (5 ml, containing ca. 100 mg N_2O_4) and the solution was stirred for another hour. Water (30 ml) was then added and the

two-phase mixture transferred to a separatory funnel. The contents of the separatory funnel were shaken and the aqueous layer was removed. The ether layer was washed with dilute sodium bicarbonate followed by water, dried over anhydrous magnesium sulfate and evaporated to give a white foam (275 mg). Crystallization of this material from ether afforded trinitro compound (21 mg, 7.6%). The noncrystalline residue possessed the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1725 (s), 1640 (m), 1540 cm^{-1} (s). Nuclear magnetic resonance spectrum: τ = 9.15, 9.02, 8.82, 8.75, 8.43, 8.35, 8.23, 6.34 and 6.23 (10:6), 5.02, 4.24, 3.80. Relative intensities of these signals were difficult to determine.

The noncrystalline material (245 mg) was subjected to chromatography on silica gel (12.5 g). Fractions 1-4, eluted with Skellysolve B (150 ml) and Skellysolve B-benzene (1:1, 50 ml) afforded an unidentified oil (8 mg).

Fractions 5-7, eluted with Skellysolve B-benzene (1:1, 150 ml) afforded an oily substance (10 mg) whose infrared spectrum showed bands at 1640 (s), 1300 (s), 850 cm^{-1} (s) characteristic of a $-\text{NO}_3$ group and at 1560 cm^{-1} (s) attributable to a NO_2 group.

Fractions 8-9, eluted with benzene (100 ml) gave a material (56 mg) which had the following spectral properties. Infrared spectrum: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1640 (w), 1540 (s), 1365 cm^{-1} (m). Nuclear magnetic resonance spectrum: τ = 9.16, 8.83, 8.81, 8.75, 8.25, 8.22, 6.33,

6.24, 5.04 (complex), 3.72. The underlined signals are attributable to the major component. Relative intensities of the signals at τ 6.24 and τ 6.33 indicated a ratio 7:5. Isolation of the major compound by crystallization or rechromatography was not successful.

Fractions 10-14, eluted with benzene (250 ml) gave material (36 mg) whose infrared spectrum (CHCl_3) showed absorption at 1720 (s), 1550 (s), 1640 cm^{-1} (w). The n.m.r. spectrum was poorly resolved. It contained signals at τ = 9.16, 9.02, 8.80, 8.75, 8.25, 6.34, 6.24, 5.7, 5.04, 3.75. Relative intensities of the signals at τ 6.24 and 6.34 were in the ratio of 3:5.

Later fractions eluted with solvents ranging from benzene-ethyl acetate (39:1) to ethyl acetate afforded intractable material (107 mg).

The material from fractions 10-14 was rechromatographed on alumina (1.8 g). Elution with benzene (20 ml) gave yellow colored material (18 mg) which possessed the following spectral properties. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 1720 (s), 1630 (w), 1610 (w), 1550 (s), 1500 (m), 1300 cm^{-1} (m). Ultraviolet spectrum: $\bigwedge_{\text{max}}^{\text{EtOH}}$ 346 m μ , broad absorption in the region 210-240 m μ . Elution with benzene-ethyl acetate (120 ml) afforded material (4 mg) which had the following spectral characteristics. Infrared spectrum: $\bigvee_{\text{max}}^{\text{CHCl}_3}$ 3600 (m), 1720 (s), 1610 (w), 1550 (m), 1500 (m), 1320 cm^{-1} (m). Ultraviolet spectrum: $\bigwedge_{\text{max}}^{\text{EtOH}}$ 362 m μ , broad absorption in the region 210-240 m μ .

Reaction of diene 82a with N_2O_4 in acetic acid.

To a solution of diene 82a (185 mg) in glacial acetic acid (10 ml) was added with stirring a solution (4 ml) of dinitrogen tetroxide (\approx 125 mg) in acetic acid in two portions over a period of 20 minutes. The resulting brownish solution was kept stirred for one hour and then diluted with water (100 ml). The organic precipitate was extracted with ether (100 ml). The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to give material (235 mg) which spontaneously crystallized during evaporation of the solvent. Separation of the crystalline material was effected by dissolving the noncrystalline mass in ether and decanting the ether. This gave 57 mg of crystalline product and 178 mg of noncrystalline product. The crystalline product was found to be identical with an authentic sample of trinitro compound 60. The noncrystalline product was subjected to chromatography on alumina (8.5 g). Fractions 1-3, eluted with benzene (90 ml) gave an unidentified oil (31 mg). Fractions 4-7, eluted with benzene (120 ml) gave material (22 mg) which crystallized from ethanol to afford dinitro compound 61 (6 mg). The noncrystalline residue contained nitroacetate 400 as judged by the infrared spectrum. Further elution with more polar solvents which included benzene-ether (85:15, 90 ml) and benzene-ether (1:1, 200 ml) gave intractable material (40 mg).

The noncrystalline residue (14 mg) from fractions 8-10 above was

the first of these is the fact that the

the second is the fact that the

the third is the fact that the

the fourth is the fact that the

the fifth is the fact that the

the sixth is the fact that the

the seventh is the fact that the

the eighth is the fact that the

the ninth is the fact that the

the tenth is the fact that the

the eleventh is the fact that the

the twelfth is the fact that the

the thirteenth is the fact that the

the fourteenth is the fact that the

the fifteenth is the fact that the

the sixteenth is the fact that the

the seventeenth is the fact that the

the eighteenth is the fact that the

the nineteenth is the fact that the

the twentieth is the fact that the

the twenty-first is the fact that the

the twenty-second is the fact that the

the twenty-third is the fact that the

the twenty-fourth is the fact that the

chromatographed on silica gel (1.5 g). Elution with Skellysolve B-benzene (1:1, 40 ml) and benzene (40 ml) gave an unidentified yellow colored material. Elution with benzene-ether (24:1, 40 ml) gave material (7 mg) which crystallized from ethanol on seeding with a crystal of nitroacetate 400. The crystalline material was identified as nitroacetate 400 by comparison of the t.l.c. behavior and the infrared spectrum with an authentic sample.

Treatment of diene 82a with HOAc-HClO₄.

A solution of diene 82a (58 mg) in glacial acetic acid (3.5 ml) containing 70% perchloric acid (3 drops) was allowed to stand at room temperature for 20 hours. The solution was diluted with water (25 ml) and extracted with chloroform (2 x 25 ml). The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to afford an oil (65 mg). This was subjected to chromatography on alumina (4 g). Elution with Skellysolve B (80 ml) and Skellysolve B-benzene (3:1, 80 ml) gave unchanged diene 82a (23 mg). Elution with Skellysolve B-benzene (1:1, 120 ml) gave an unidentified material (3 mg). Elution with benzene (120 ml) gave an oil (24 mg) which was composed of endo acetate 76b and acetate 402 as judged by the infrared and the n.m.r. spectra. The n.m.r. spectrum showed signals at τ 9.36, 9.15, 8.97 (d., $J \approx 7$ c.p.s.), 8.84, 8.43, 8.34 (poorly resolved), 8.06, 6.35, 5.41, 5.44, 4.68. The underlined signals are attributable to acetate 76b.

the first of these is the fact that the

the second

the third

the fourth

the fifth

the sixth

the seventh

the eighth

the ninth

the tenth

the eleventh

the twelfth

the thirteenth

the fourteenth

the fifteenth

the sixteenth

the seventeenth

the eighteenth

the nineteenth

the twentieth

the twenty-first

the twenty-second

the twenty-third

In an earlier experiment similar treatment of diene 82a (48 mg) afforded 14 mg of the acetate mixture. This was hydrolyzed by refluxing in methanolic potassium hydroxide. The product was first treated with ethereal diazomethane and then chromatographed over alumina (1.5 g). Elution with benzene-ether (3:1, 50 ml) gave material (6 mg) which crystallized from Skellysolve B on seeding with a crystal of alcohol 76a. The crystalline product was identified as alcohol 76a by t.l.c. and infrared comparison.

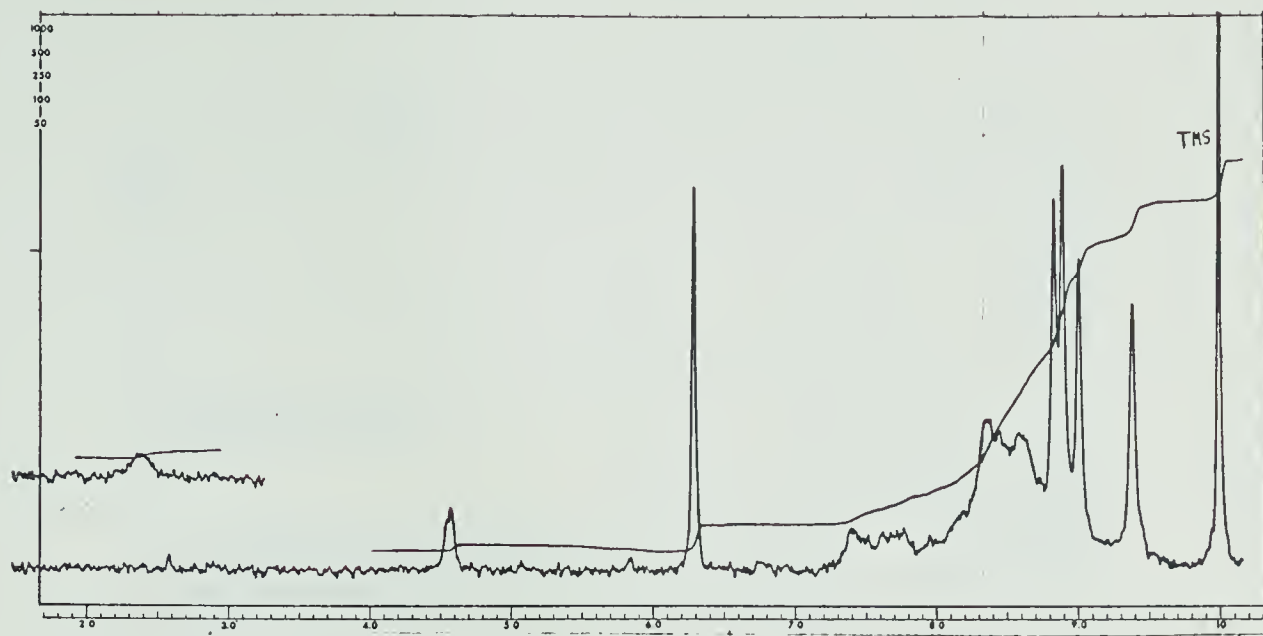


Figure 1. Nuclear magnetic resonance spectrum of adduct 31.

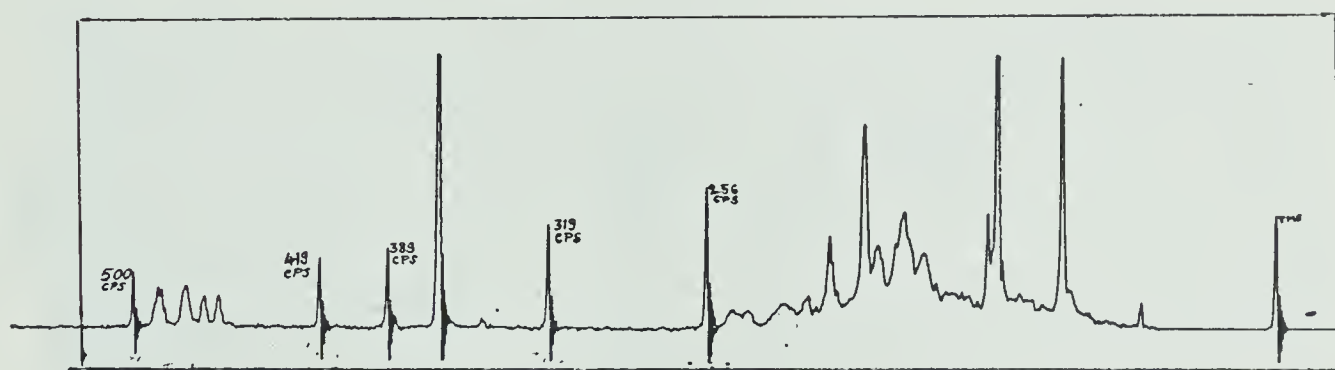


Figure 2. Nuclear magnetic resonance spectrum of the isopropenyl lactone 37.

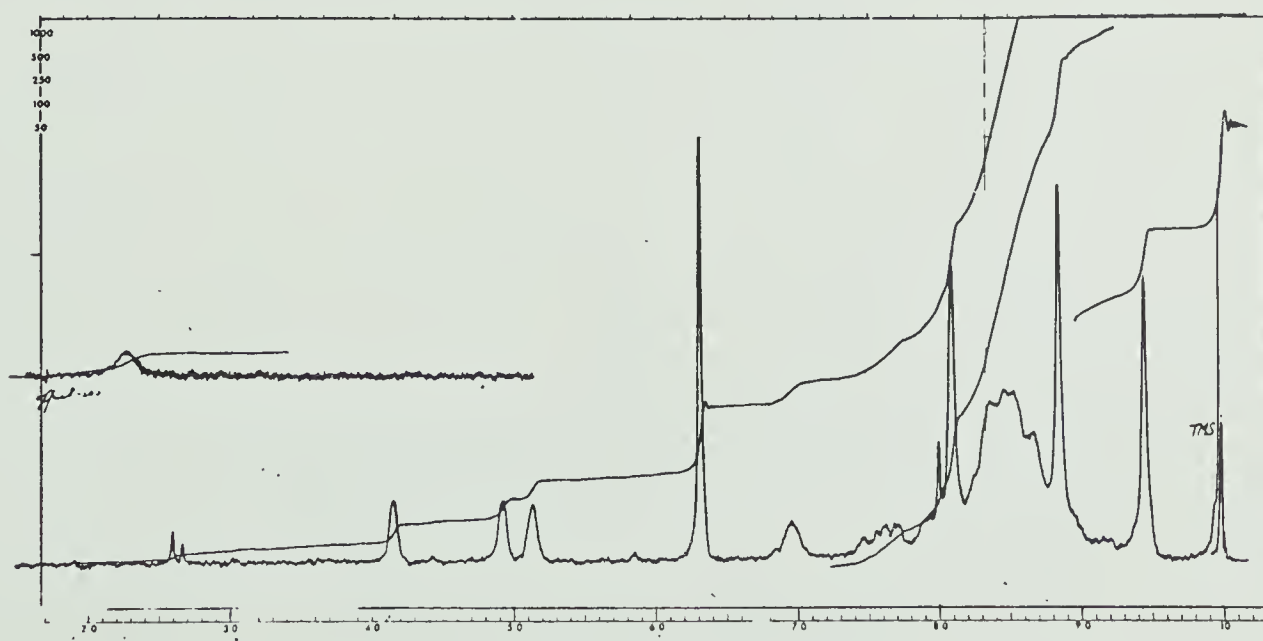


Figure 3. Nuclear magnetic resonance spectrum of the diene acid 38



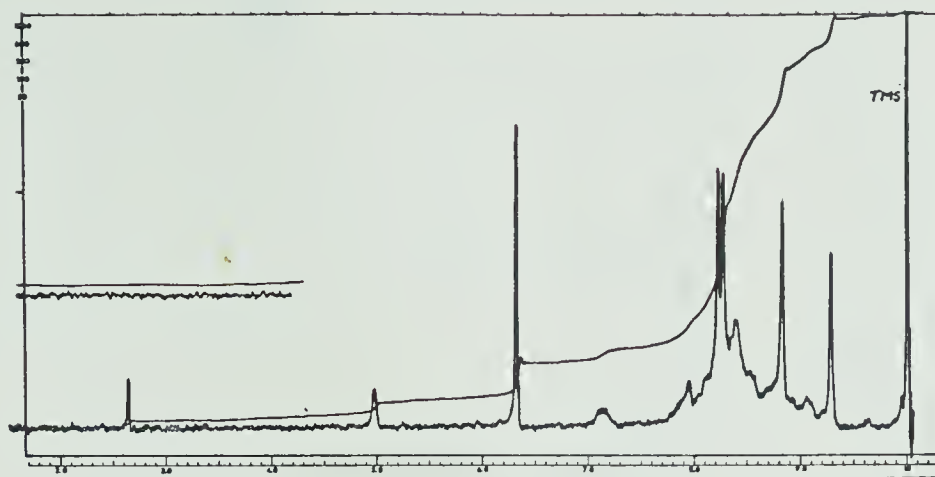


Figure 4. Nuclear magnetic resonance spectrum of isopropylidene lactone 39

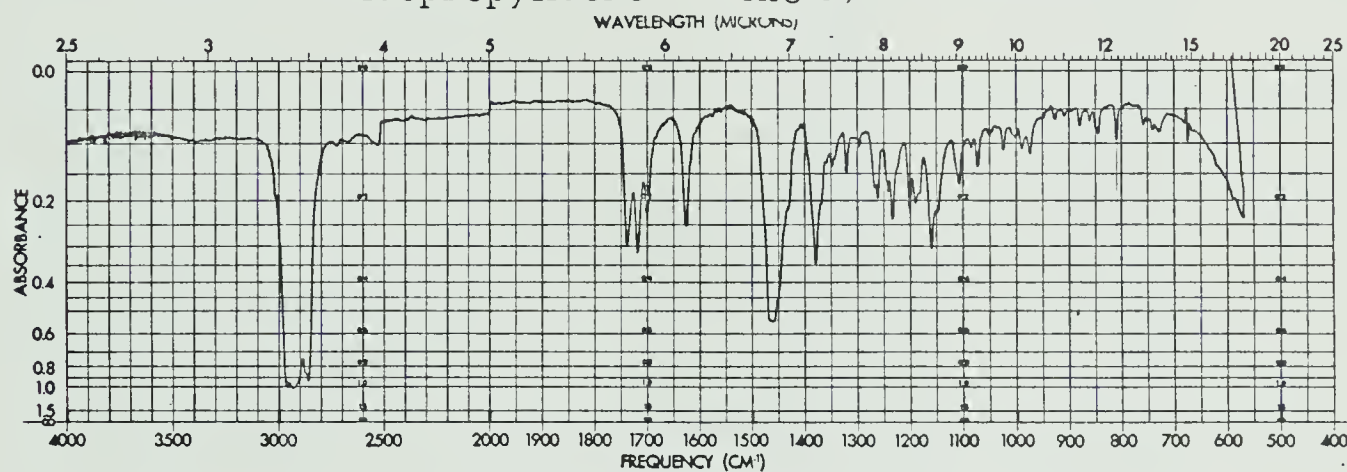


Figure 5. Infrared spectrum (nujol) of the α,β unsaturated ketone 41.



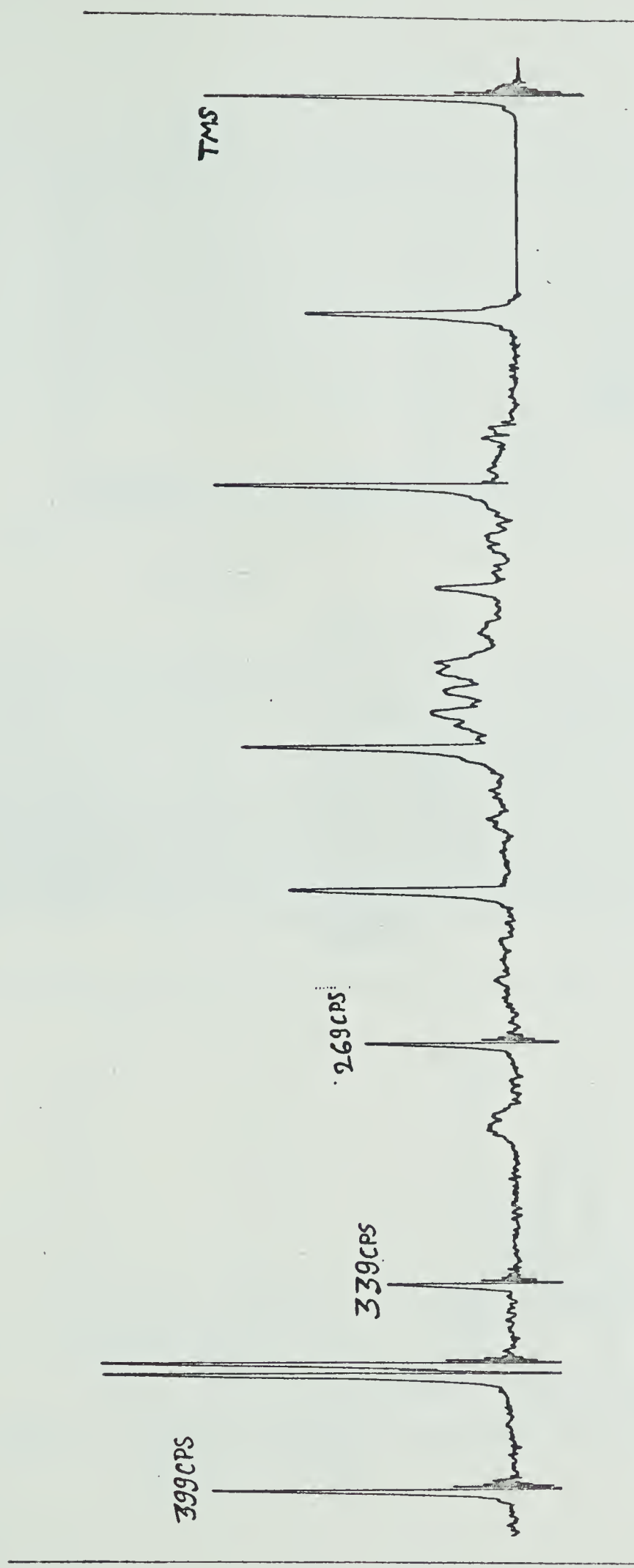


Figure 6. Nuclear magnetic resonance spectrum of the α,β unsaturated ketone 41.

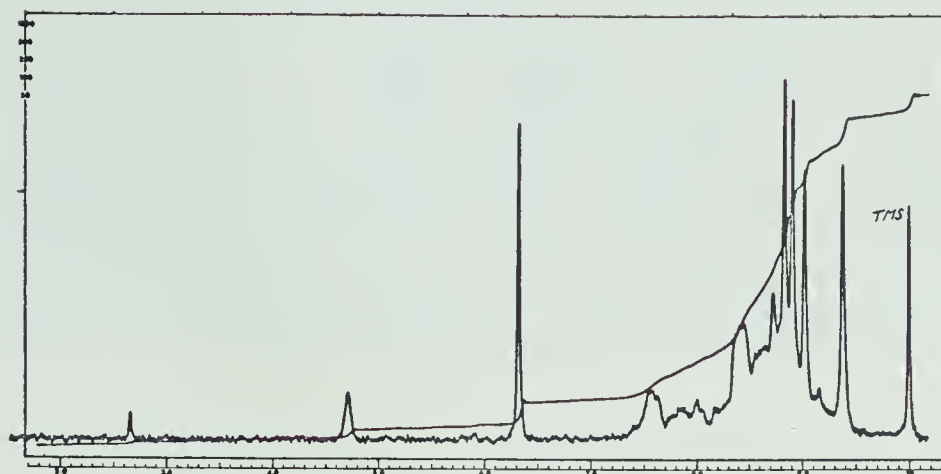


Figure 7. Nuclear magnetic resonance spectrum of the amine 29.

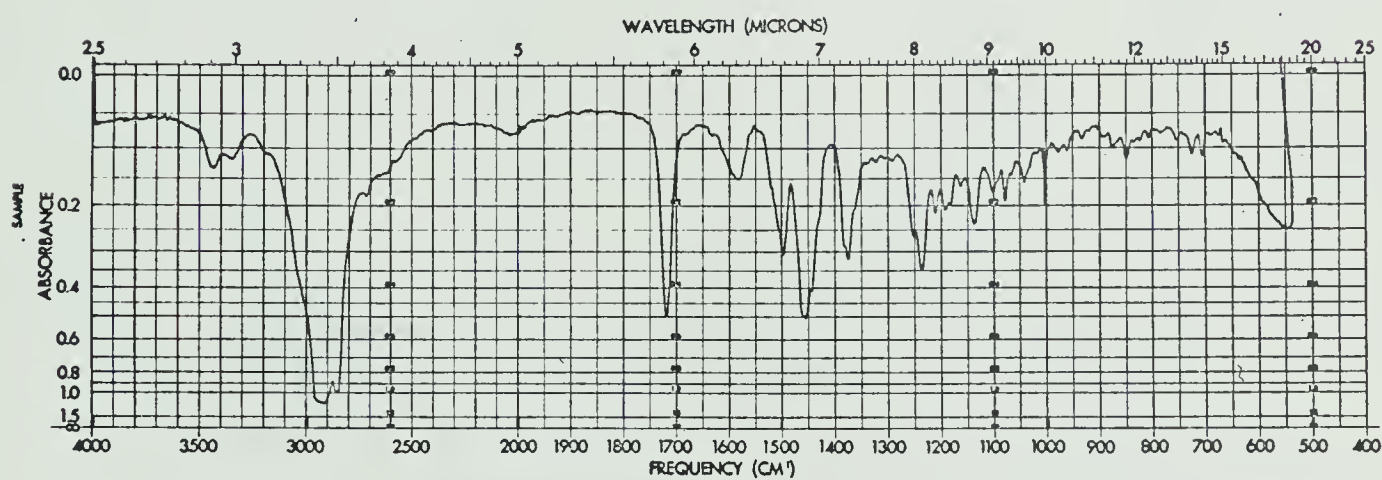


Figure 8. Infrared spectrum (nujol) of the amine hydrochloride 50.

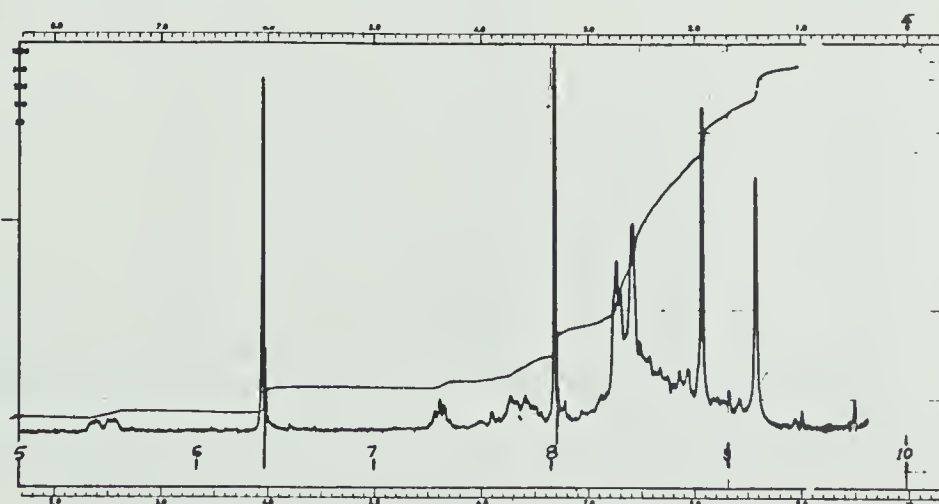


Figure 9. Nuclear magnetic resonance spectrum of the acetate 402 (52).

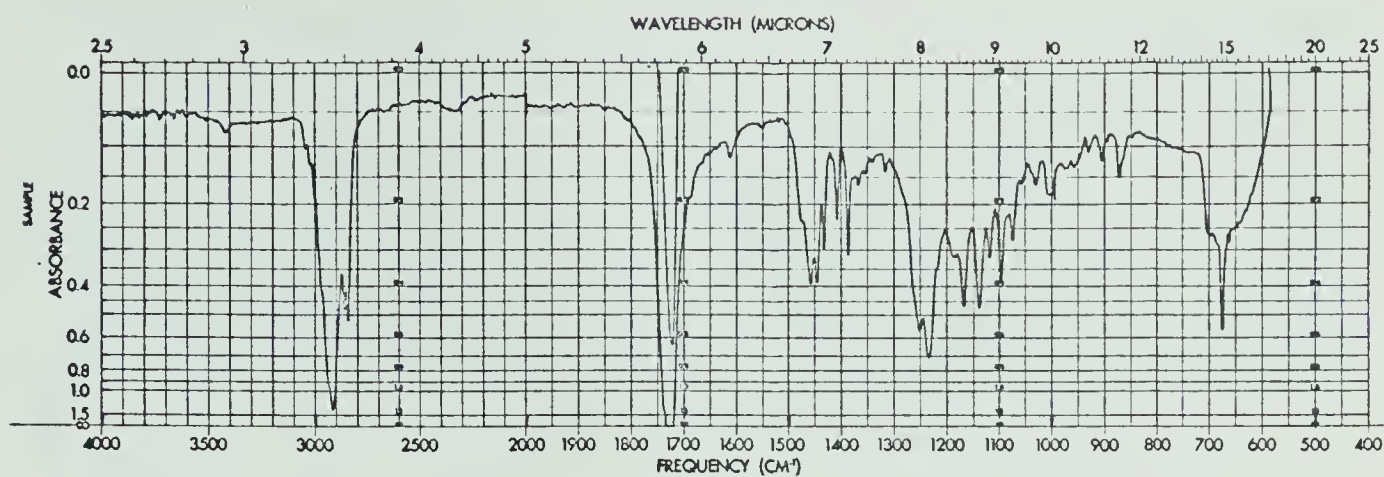


Figure 10. Infrared spectrum (CCl₄) of the ketoolefin 56.

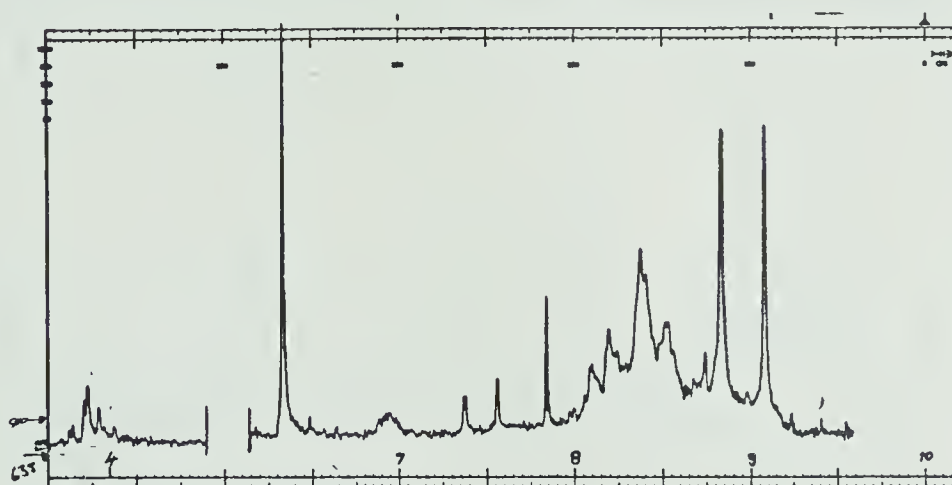


Figure 11. Nuclear magnetic resonance spectrum of the ketoolefin 56.

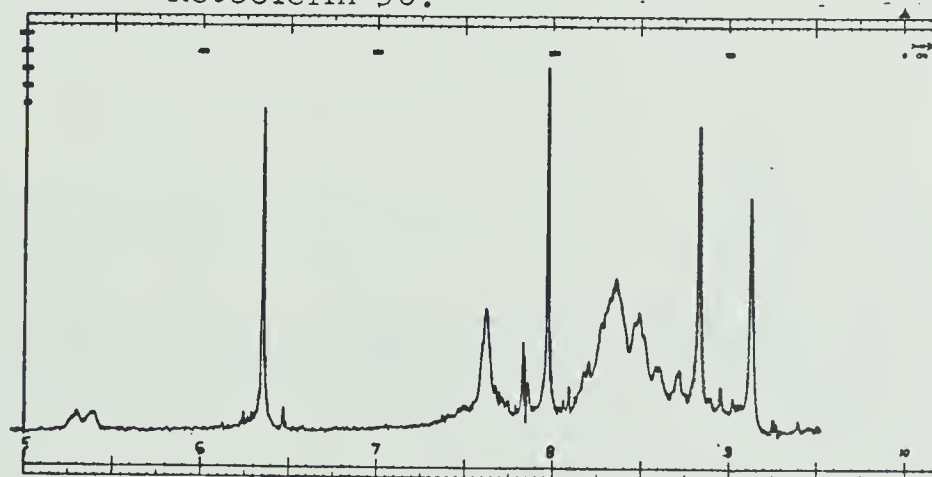


Figure 12. Nuclear magnetic resonance spectrum of the ketoacetate 376 (55a).

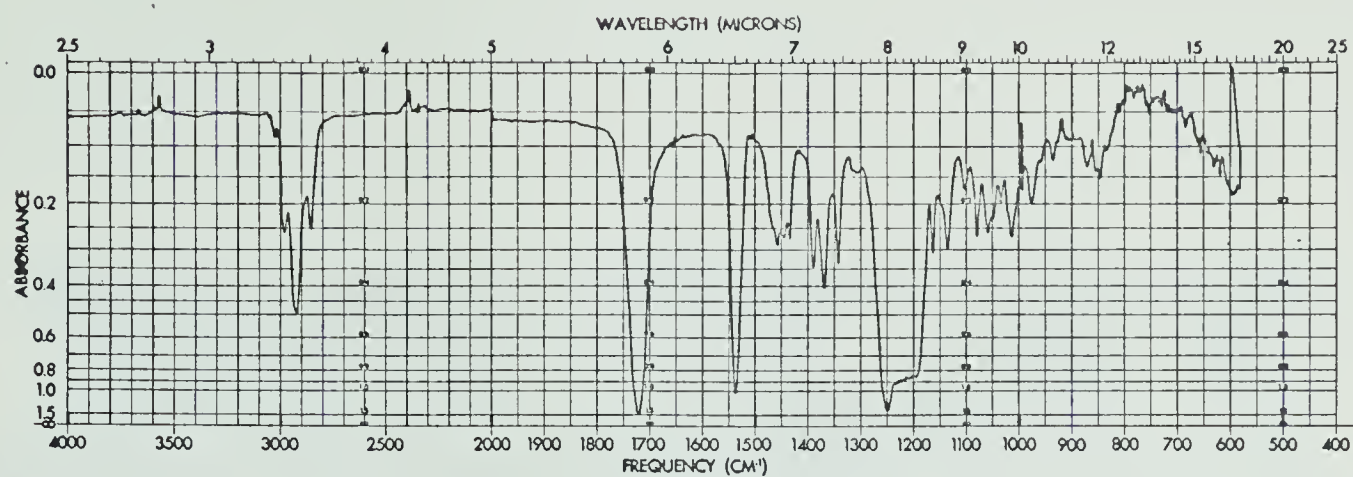


Figure 13. Infrared spectrum (CHCl_3) of the nitroacetate 400 (57).

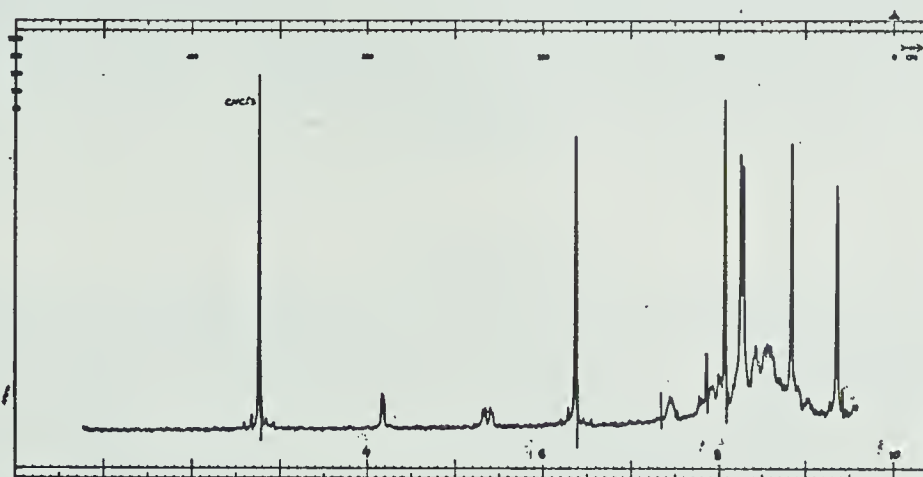


Figure 14. Nuclear magnetic resonance spectrum of the nitroacetate 400 (57).



Figure 15. Nuclear magnetic resonance spectrum of compound 62.



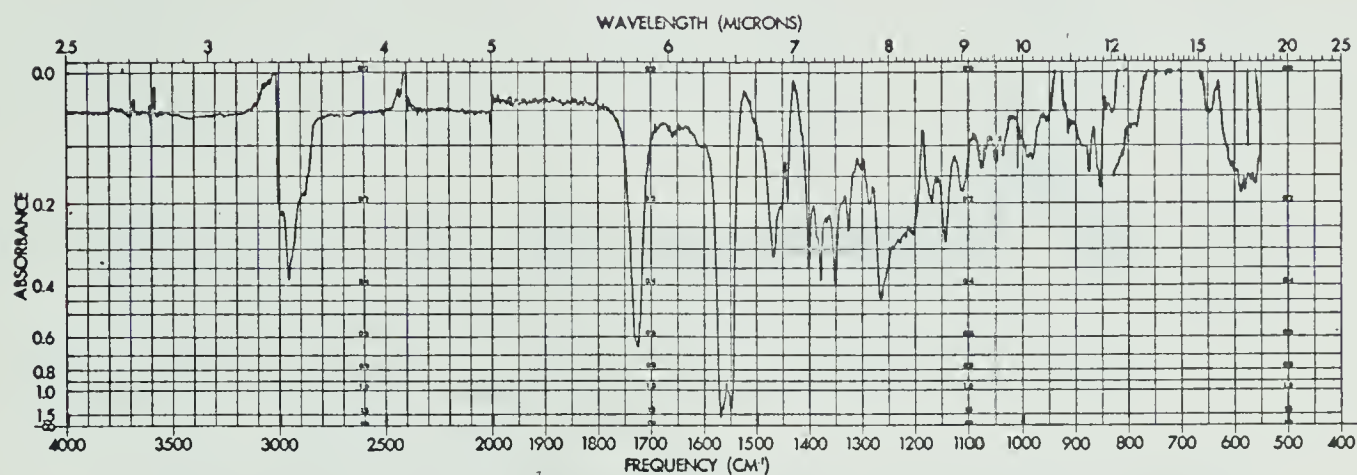


Figure 16. Infrared spectrum (CHCl_3) of the trinitro compound 60.

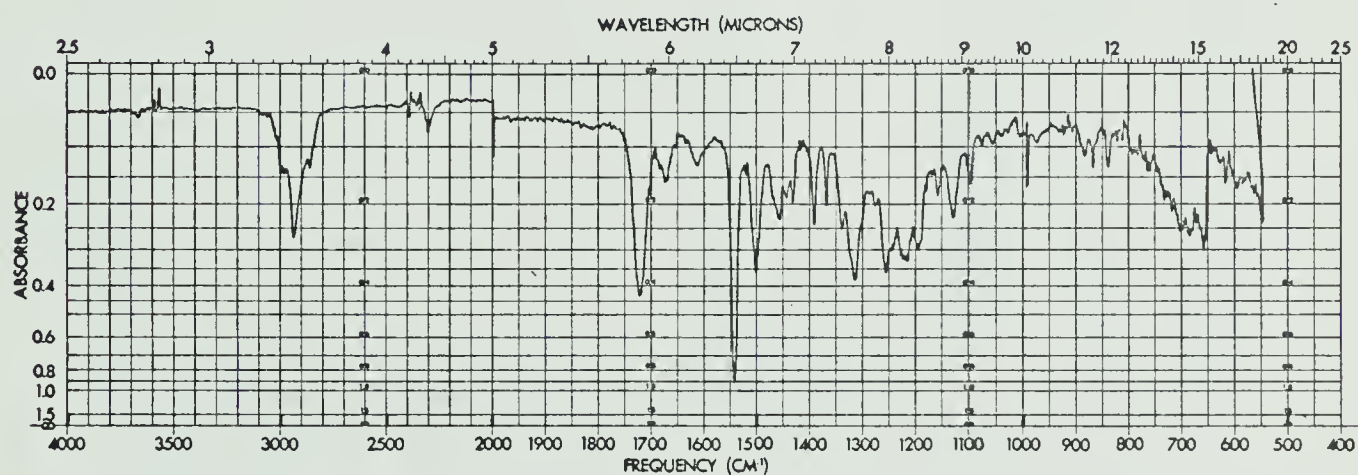


Figure 17. Infrared spectrum (CHCl_3) of the dinitro compound 61.

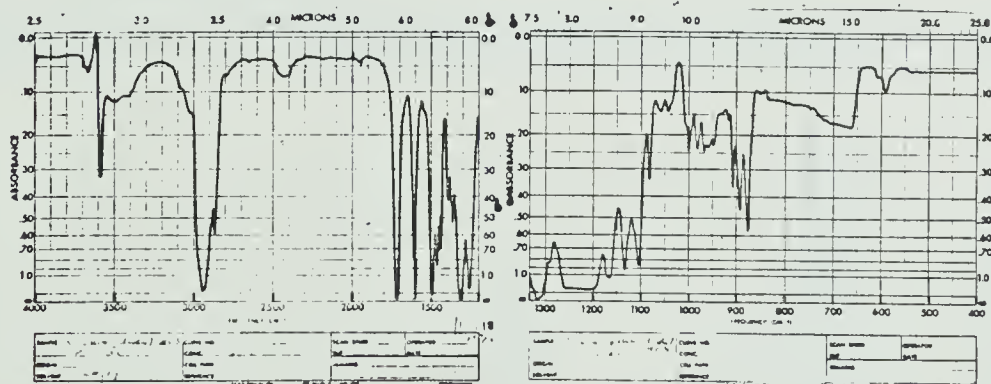


Figure 18. Infrared spectrum (CHCl_3) of the nitroalcohol 73.



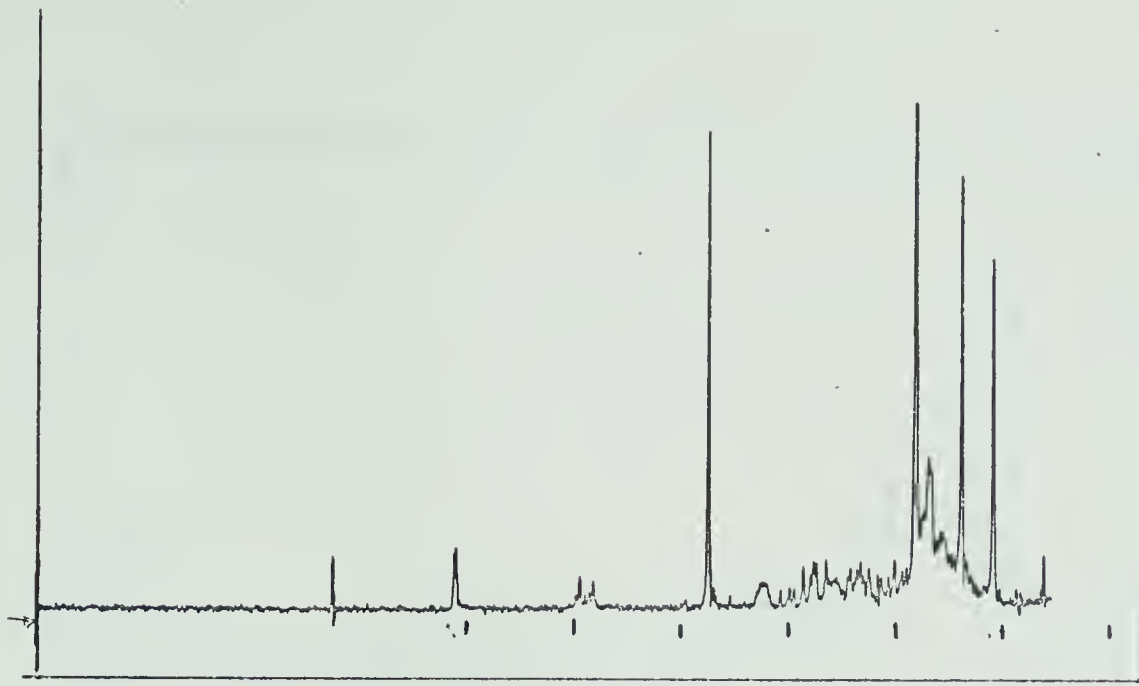


Figure 19. Nuclear magnetic resonance spectrum of the trinitro compound 60.

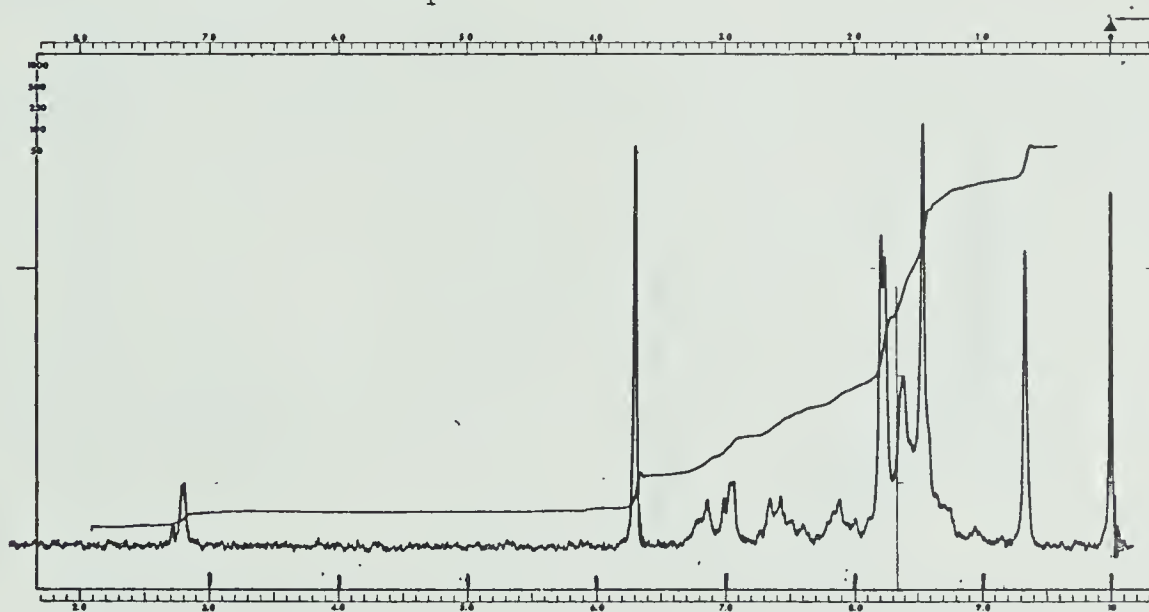


Figure 20. Nuclear magnetic resonance spectrum of the dinitro compound 61.

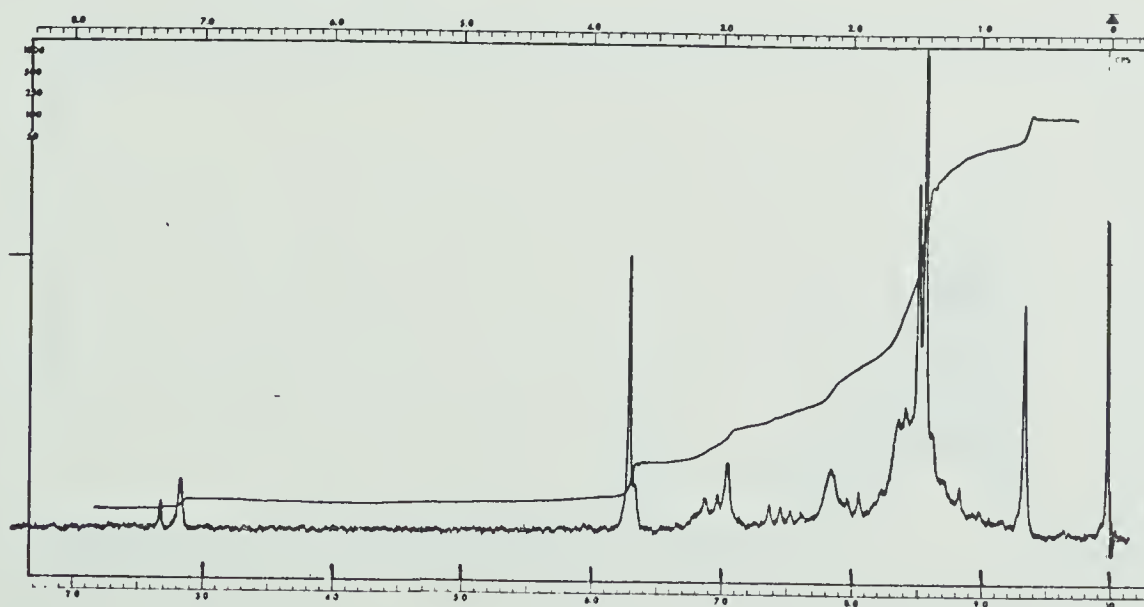


Figure 21. Nuclear magnetic resonance spectrum of the nitroalcohol 73.



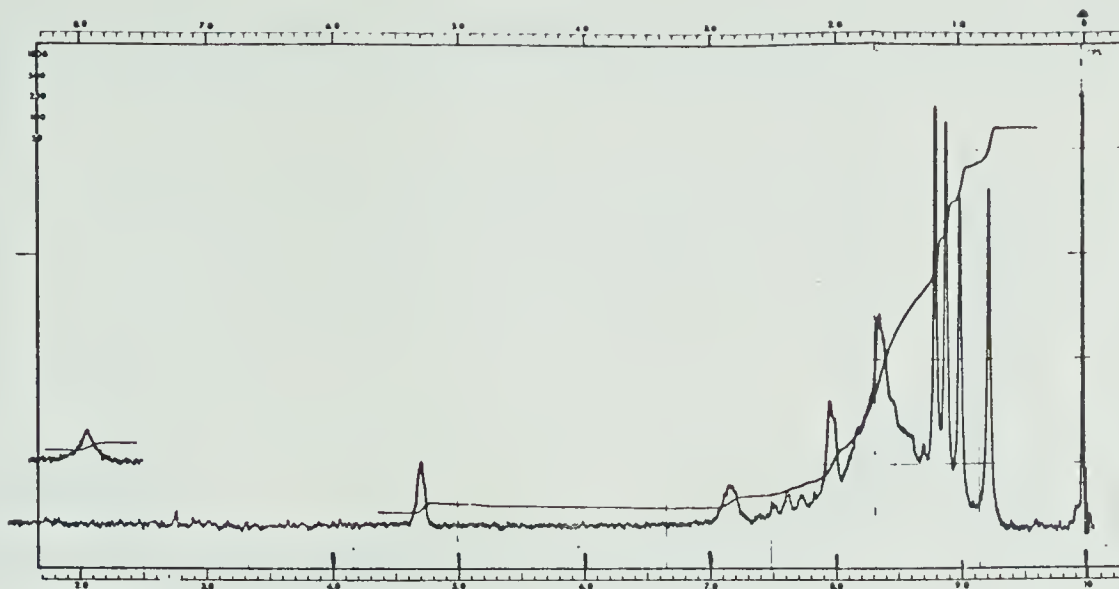


Figure 22. Nuclear magnetic resonance spectrum of the ketoacid 80a.

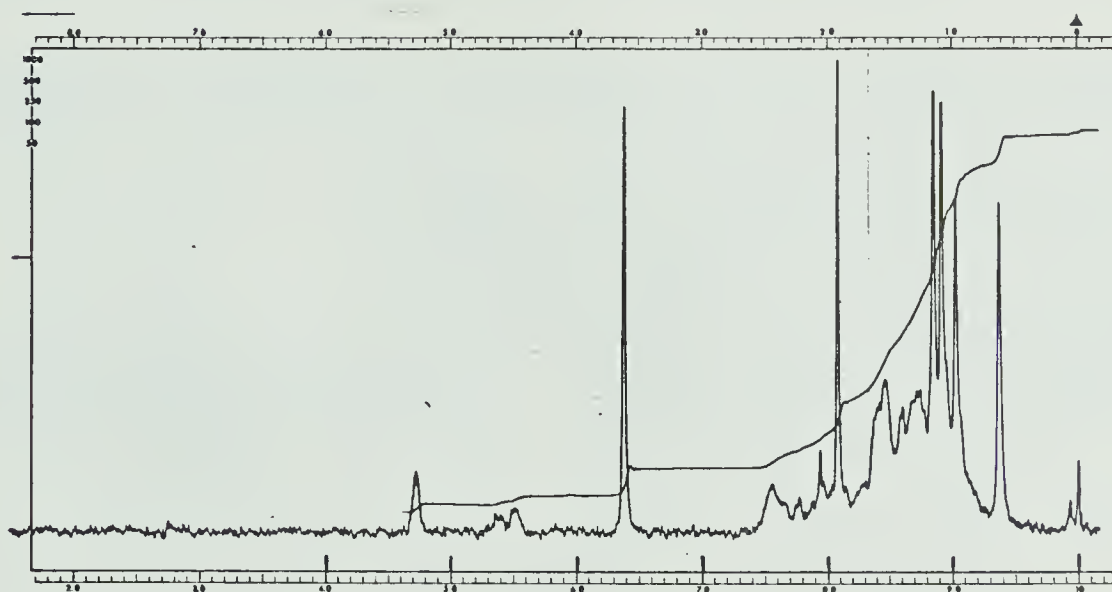


Figure 23. Nuclear magnetic resonance spectrum of the endo acetate 76b.

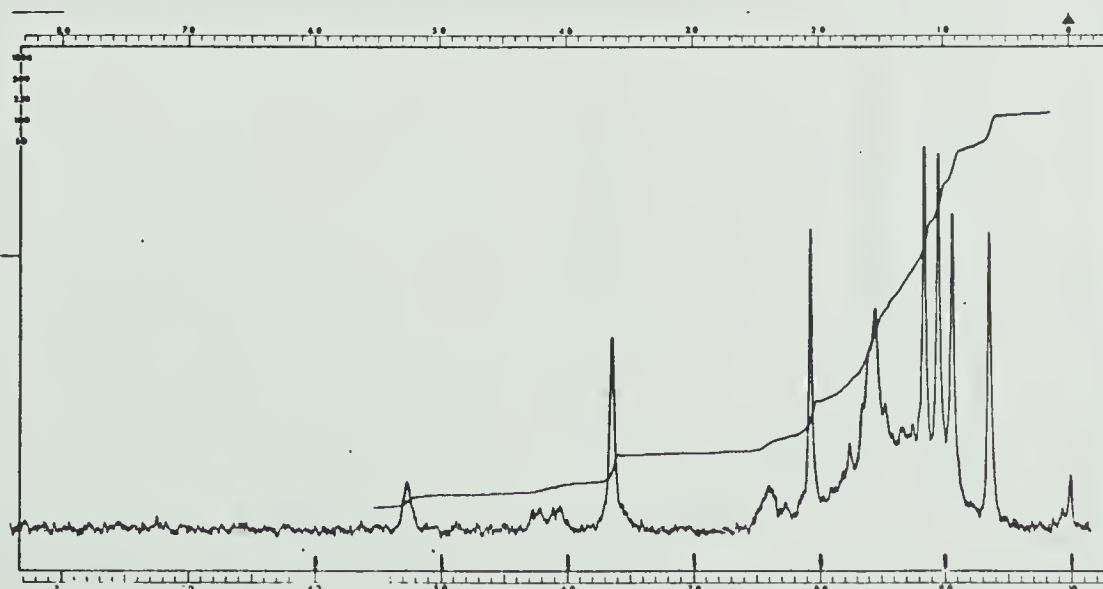


Figure 24. Nuclear magnetic resonance spectrum of the exo acetate 81b.



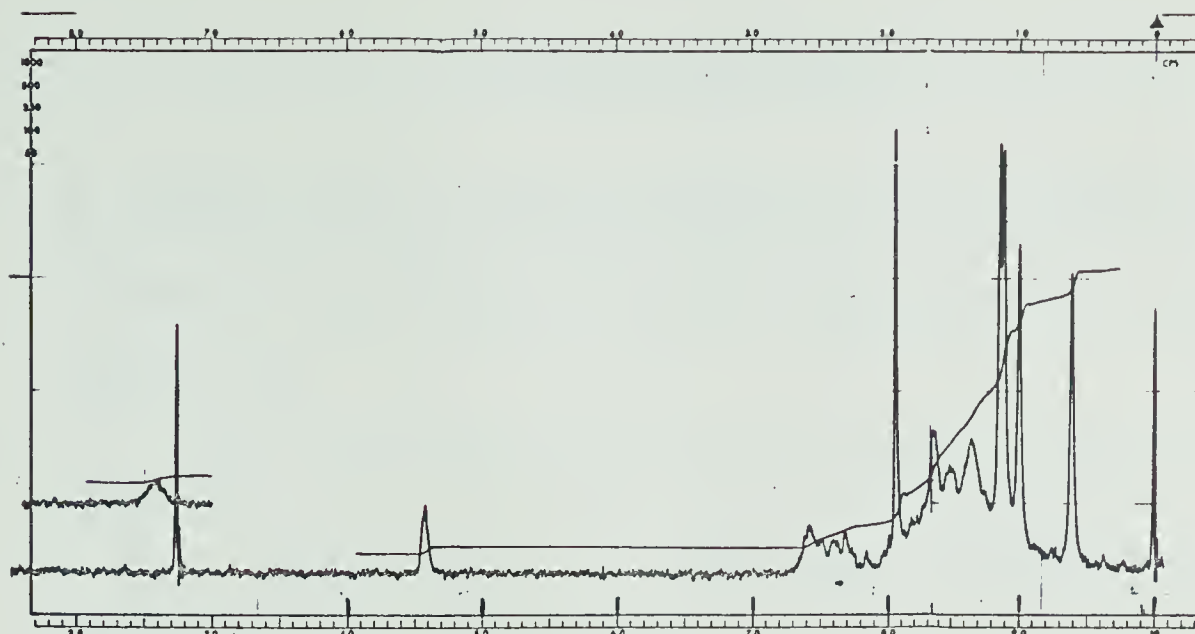


Figure 25. Nuclear magnetic resonance spectrum of the adduct 77a.

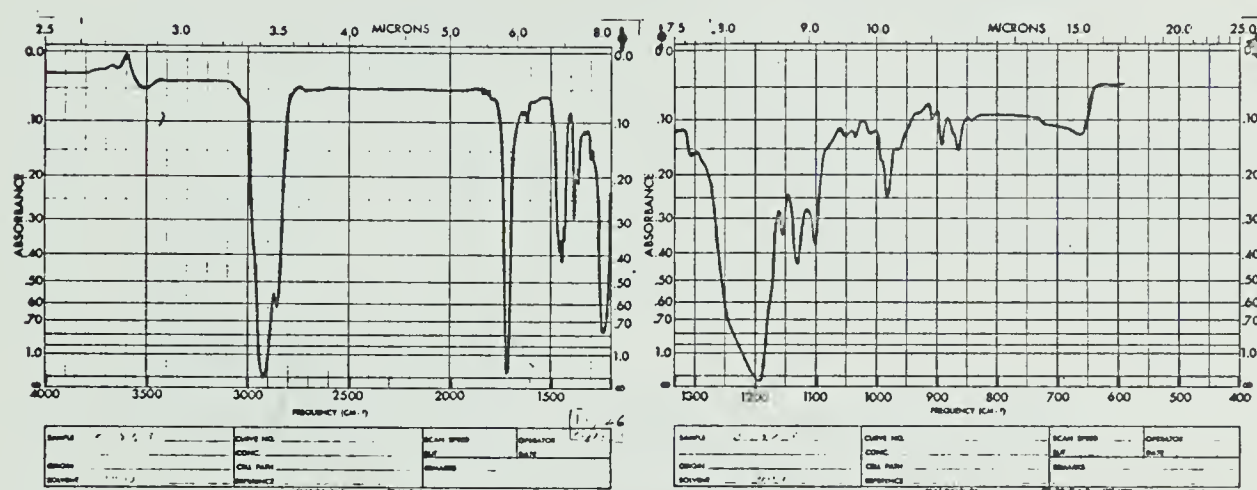


Figure 26. Infrared spectrum (CHCl_3) of the diene 82a.

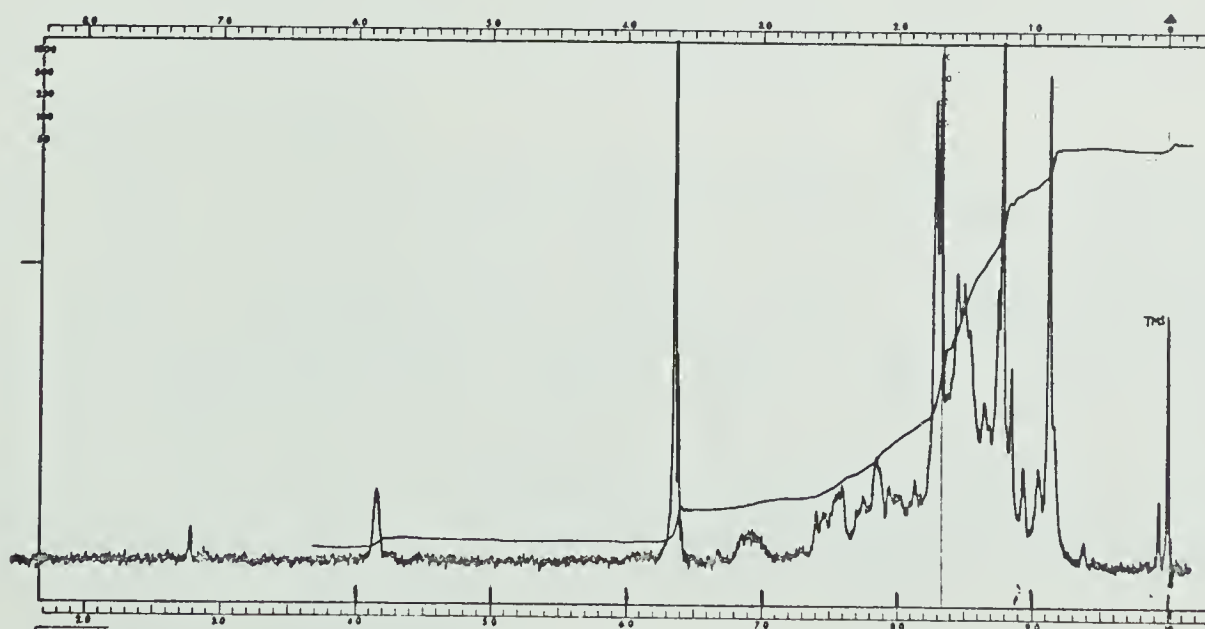


Figure 27. Nuclear magnetic resonance spectrum of the diene 82a.



R E F E R E N C E S

1. K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products" Vol. XVI, Springer-Verlag, Vienna, 1958, p. 26.
2. E. S. Stern, "The Alkaloids, Chemistry and Physiology", Vol. VII, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1960, p. 473
3. a) S. W. Pelletier, Tetrahedron, 14, 76 (1961).
b) S. W. Pelletier, Experientia, 20, 1, (1964).
4. W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, J. Am. Chem. Soc., 89, 1483, 1499 (1967) and references cited therein.
5. M. Przybylska, Can. J. Chem., 40, 566, (1962).
6. L. Marion, "The Chemistry of Natural Products" 2, I.U.P.A.C., 1962, p. 621.
7. O. Achmatowicz, Jr., Y. Tsuda, and L. Marion, Can. J. Chem. 43, 2336 (1965).
8. a) M. Przybylska and L. Marion, Can. J. Chem., 34, 185 (1956).
b) M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959).
9. M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).
10. R. Aneja and S. W. Pelletier, Tetrahedron Letters, 669 (1964).
11. a) K. Wiesner, K. K. Chan, and C. Demerson, Tetrahedron Letters, 2893 (1965).

THE HISTORY OF THE

REIGN OF KING CHARLES THE FIRST

IN THE YEAR 1649

BY JOHN BURNET

OF THE UNIVERSITY OF OXFORD

IN TWO VOLUMES

THE FIRST

VOLUME

IN TWO VOLUMES

THE SECOND

VOLUME

IN TWO VOLUMES

THE THIRD

VOLUME

IN TWO VOLUMES

THE FOURTH

VOLUME

THE FIFTH

VOLUME

THE SIXTH

VOLUME

THE SEVENTH

VOLUME

11. b) K. Wiesner and J. Santroch, Tetrahedron Letters, 5939 (1966).
12. K. Wiesner, M. Götz, D. L. Simmons and L. R. Fowler, Coll. Czech. Chem. Commun. 28, 2462 (1963).
13. E. Wenkert, Chem. and Ind. (London), 282 (1955).
14. a) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and acetogenins", W. A. Benjamin, Inc. 1964, New York, p. 420.
b) J. B. Hendrickson, "The Molecules of Nature", W. A. Benjamin, Inc., New York, 1965, p. 37.
15. B. A. Nagsampagi, L. Yankov and S. Dev, Tetrahedron Letters, 189 (1967).
16. a) W. A. Ayer, C. E. McDonald, and G. G. Iverach, Tetrahedron Letters, 1095 (1963).
17. W. B. Whalley, Tetrahedron, 18, 43 (1962).
18. a) R. C. Cookson, and M. E. Trevett, J. Chem. Soc., 3121 (1956).
b) Z. Valenta and K. Wiesner, Chem. and Ind. (London), 354 (1956).
19. a) E. H. Herbert, and G. W. Kirby, Tetrahedron Letters, 1505 (1963).
b) M. H. Benn and J. May, Experientia, 20, 252 (1964).
20. L. H. Zalkow, and N. N. Girotra, J. Org. Chem., 28, 2037 (1963).
21. a) W. C. Wildman and D. R. Saunders, J. Am. Chem. Soc., 76, 946 (1954).
b) M. L. Goering, R. W. Greiner, and M. F. Sloan, J. Am. Chem. Soc., 83, 1391 (1961).

The first part of the paper discusses the importance of the study and the objectives of the research. It also outlines the methodology used in the study and the results obtained. The second part of the paper discusses the implications of the study and the conclusions drawn from the research. It also provides a summary of the findings and a list of references.

The study was conducted in a laboratory setting and involved the use of a series of tests to measure the performance of the system. The results of the tests were compared to the theoretical predictions and the conclusions drawn from the research. The study found that the system performed well under the conditions tested and that the theoretical predictions were generally accurate.

The implications of the study are that the system can be used in a variety of applications and that the results of the research can be used to improve the design of the system. The conclusions drawn from the research are that the system is a viable option for the application and that the results of the research can be used to improve the design of the system.

The study was conducted in a laboratory setting and involved the use of a series of tests to measure the performance of the system. The results of the tests were compared to the theoretical predictions and the conclusions drawn from the research. The study found that the system performed well under the conditions tested and that the theoretical predictions were generally accurate.

The implications of the study are that the system can be used in a variety of applications and that the results of the research can be used to improve the design of the system. The conclusions drawn from the research are that the system is a viable option for the application and that the results of the research can be used to improve the design of the system.

22. A. Gagneux and C. A. Grob, *Helv. Chim. Acta.* 42, 1753 (1959).
23. R. B. Kaplan, and H. Shechter, *J. Org. Chem.*, 26, 982 (1961).
24. W. L. Meyer, and R. W. Huffman, *Tetrahedron Letters*, 691 (1962).
25. W. D. Lloyd, and G. W. Hedrik, *J. Org. Chem.* 26, 2029 (1961).
26. R. Huisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkenes"
Ed. S. Patai, Interscience Publishers, 1964, p. 908.
27. W. A. Ayer, C. E. McDonald and J. B. Stothers, *Can. J. Chem.*
41, 1113 (1963).
28. N. J. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone,
and W. Herz, *J. Org. Chem.* 29, 1017 (1964).
29. W. A. Ayer, and C. E. McDonald, *Can. J. Chem.* 43, 1429 (1965).
30. R. Criegee "Oxidation in Organic Chemistry", Ed. K. B. Wieberg,
Academic Press, 1965, p. 337.
31. J. H. Holum, *J. Org. Chem.* 26, 4814 (1961).
32. K. Nakanishi "Infrared Absorption Spectroscopy", Holden-Day Inc.,
San Francisco, 1964, p. 42.
33. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic
Compounds", Prentice-Hall Inc., 1965, p. 11.
34. N. S. Bhacca, and D. H. Williams "Applications of NMR Spectroscopy
in Organic Chemistry", Holden-Day, Inc., 1964, p. 112.
35. H. Wolff "Organic Reactions" Vol. III, p. 307.
36. R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Am. Chem.*
Soc., 72, 4359 (1950).

The first part of the paper discusses the importance of maintaining accurate records of all transactions. It is essential for the company to have a clear and concise system in place to ensure that all financial data is properly documented and accessible. This will help in the preparation of financial statements and provide a basis for decision-making.

The second part of the paper focuses on the role of the accounting department in the overall management of the company. The accounting department is responsible for providing accurate and timely financial information to management, which is crucial for the company's success. It also plays a key role in ensuring compliance with applicable laws and regulations.

The third part of the paper discusses the importance of budgeting and financial planning. A well-defined budget is essential for the company to set its financial goals and monitor its performance. It also helps in identifying potential risks and opportunities, allowing management to make informed decisions.

The fourth part of the paper discusses the importance of internal controls. Internal controls are designed to prevent and detect errors and fraud, ensuring the integrity of the company's financial data. It is essential for the company to have a strong internal control system in place to protect its assets and maintain the trust of its stakeholders.

The fifth part of the paper discusses the importance of financial reporting. Financial reports provide management and stakeholders with the information they need to make informed decisions. It is essential for the company to have a clear and concise system in place to ensure that all financial data is properly documented and accessible.

The sixth part of the paper discusses the importance of financial analysis. Financial analysis is the process of evaluating the company's financial performance and identifying areas for improvement. It is essential for the company to have a strong financial analysis system in place to help management make informed decisions.

The seventh part of the paper discusses the importance of financial forecasting. Financial forecasting is the process of predicting the company's future financial performance. It is essential for the company to have a strong financial forecasting system in place to help management make informed decisions.

The eighth part of the paper discusses the importance of financial risk management. Financial risk management is the process of identifying and managing the company's financial risks. It is essential for the company to have a strong financial risk management system in place to protect its assets and maintain the trust of its stakeholders.

The ninth part of the paper discusses the importance of financial compliance. Financial compliance is the process of ensuring that the company's financial practices comply with applicable laws and regulations. It is essential for the company to have a strong financial compliance system in place to avoid legal penalties and maintain the trust of its stakeholders.

The tenth part of the paper discusses the importance of financial transparency. Financial transparency is the process of providing management and stakeholders with clear and concise financial information. It is essential for the company to have a strong financial transparency system in place to build trust and maintain the integrity of its financial data.

37. a) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. Gribi, H. Gschwend, E. F. Meyer, M. Pisaro, and R. Scheffold, *Angew. Chem. Int. Ed.* 3, 490, (1964).
b) H. Muxfeldt, and W. Rogalski, *J. Am. Chem. Soc.*, 87, 933 (1965).
38. a) J. B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Commun.* 165, (1965).
b) R. W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 2945 (1965).
39. P. A. S. Smith, "Organic Reactions", Vol. III, p. 337.
40. N. G. Gaylord, "Reduction with Complex Metal Hydrides", Interscience Publishers, New York, 1965.
41. R. J. Baumgarten, *J. Chem. Ed.* 43, 398 (1966).
42. J. D. Roberts, and M. Caseiro, "Basic Principles of Organic Chemistry", W. A. Benjamin, New York, p. 665.
43. K. Tori, Y. Takano, and K. Kitahonoki, *Ber.*, 97, 2798 (1964).
44. K. Bowden, E. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
45. L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne, *J. Am. Chem. Soc.*, 74, 3309 (1952).
46. R. H. Bible, "Interpretation of NMR Spectra", Plenum Press, New York, 1965, p. 82.
47. N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day Inc., San Francisco, 1964, p. 110.

48. R. T. Aplin, M. Fischer, D. Becher, H. Budzikiewicz, and C. Djerassi, J. Am. Chem. Soc., 87, 4888 (1965).
49. A. A. Griswold, and P. S. Starcher, J. Org. Chem., 31, 357 (1966).
50. C. E. Anagnostopoulos, and L. F. Fieser, J. Am. Chem. Soc., 76, 532, (1954).
51. a) H. Shechter, and F. Conrad, J. Am. Chem. Soc., 76, 2716 (1954).
b) A. T. Nielson, J. Org. Chem., 27, 2001 (1962).
52. R. M. Dodson and B. Riegel, J. Org. Chem., 13, 424 (1948).
53. A. T. Nielson, J. Org. Chem., 27, 1998 (1962).
54. E. I. Snyder, J. Am. Chem. Soc., 85, 2624 (1963).
55. K. Bieman, "Mass Spectrometry, Organic Chemical Applications" McGraw-Hill, New York, 1962.
56. E. H. White, J. Am. Chem. Soc., 77, 6008, 6014 (1955).
57. R. A. Bell, R. E. Ireland, and L. N. Mander, J. Org. Chem., 31, 2536 (1966).
58. A. Nickon, and A. S. Hill, J. Am. Chem. Soc., 86, 1152 (1964).
59. H. Hasegawa, Y. Sato, T. Tanaka, and K. Tsuda, Chem. Pharm. Bull. (Tokyo) 9, 740 (1961).
60. G. Saucy, H. Els, F. Miksch, and A. Furst, Helv. Chim. Acta, 49, 1529 (1966).
61. C. E. McDonald, Ph.D. Thesis, Univ. of Alberta (1964), p. 108.

1. The first part of the paper is devoted to the study of the properties of the function $f(x)$.

2. In the second part, we consider the case when $f(x)$ is a polynomial.

3. The third part is devoted to the study of the properties of the function $f(x)$.

4. The fourth part is devoted to the study of the properties of the function $f(x)$.

5. The fifth part is devoted to the study of the properties of the function $f(x)$.

6. The sixth part is devoted to the study of the properties of the function $f(x)$.

7. The seventh part is devoted to the study of the properties of the function $f(x)$.

8. The eighth part is devoted to the study of the properties of the function $f(x)$.

9. The ninth part is devoted to the study of the properties of the function $f(x)$.

10. The tenth part is devoted to the study of the properties of the function $f(x)$.

11. The eleventh part is devoted to the study of the properties of the function $f(x)$.

12. The twelfth part is devoted to the study of the properties of the function $f(x)$.

13. The thirteenth part is devoted to the study of the properties of the function $f(x)$.

14. The fourteenth part is devoted to the study of the properties of the function $f(x)$.

15. The fifteenth part is devoted to the study of the properties of the function $f(x)$.

16. The sixteenth part is devoted to the study of the properties of the function $f(x)$.

17. The seventeenth part is devoted to the study of the properties of the function $f(x)$.

18. The eighteenth part is devoted to the study of the properties of the function $f(x)$.

19. The nineteenth part is devoted to the study of the properties of the function $f(x)$.

20. The twentieth part is devoted to the study of the properties of the function $f(x)$.

21. The twenty-first part is devoted to the study of the properties of the function $f(x)$.

22. The twenty-second part is devoted to the study of the properties of the function $f(x)$.

23. The twenty-third part is devoted to the study of the properties of the function $f(x)$.

24. The twenty-fourth part is devoted to the study of the properties of the function $f(x)$.

62. J. A. Berson, and S. Suzuki, J. Am. Chem. Soc., 81, 4088 (1959).
63. a) L. H. Zalkow, M. V. Kulkarni, and N. N. Girotra, J. Org. Chem., 30, 1679 (1965).
- b) N. Langlois, and B. Gastambide, Bull. Soc. Chim. Fr., 2966 (1965).
64. R. Levine, and J. R. Stephens, J. Am. Chem. Soc. 72, 1642 (1950).
65. A. Rosowsky, "Heterocyclic Compounds with Three and Four Membered Rings", Part I. Interscience Publishers, Ed. A. Weissberg (1964), p. 456.
66. P. D. Bartlett, and B. E. Tate, J. Am. Chem. Soc., 78, 2473 (1956).
67. a) J. Smrt, and F. Sorm, Chem. Listy. 48, 217 (1954). C. A. 49, 2311b, (1955).
- b) F. Johnston, and L. W. Newton, U. S. Pat. 2,395,930 (1946), C. A., 40, 4078, (1946).
68. P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, Inc., San Francisco, 1965.
69. A. A. Youssef, M. E. Baum, and H. H. Walborsky, J. Am. Chem. Soc., 81, 4709 (1959).
70. P. V. Schleyer, D. S. Trifan, and R. Bacskai, J. Am. Chem. Soc., 80, 6691 (1958).
71. H. Tanida, T. Tsuji, and T. Irie, J. Am. Chem. Soc. 89, 1953 (1967).

72. F. C. Chang, and N. F. Wood, Tetrahedron Letters, 2969 (1964).
73. a) R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, J. Org. Chem., 21, 478 (1956).
b) D. Dvornik, and O. E. Edwards, Tetrahedron, 14, 54 (1961).
74. W. L. Meyer, D. D. Cameron, and W. S. Johnson, J. Org. Chem., 27, 1130 (1962).
75. E. Wenkert, and J. W. Chamberlin, J. Am. Chem. Soc., 81, 688 (1959).
76. P. A. S. Smith, "Open Chain Nitrogen Compounds", W. A. Benjamin, 1965, Vol. I, p. 7.
77. N. Levy, C. W. Scaife, and A. E. Wilder-Smith, J. Chem. Soc., 52 (1948).
78. H. Shechter, J. J. Gardikes, T. S. Cantrell, and G. V. D. Tiers, J. Am. Chem. Soc., 89, 3005 (1967).
79. C. K. Ingold, and E. H. Ingold, Nature, 159, 743 (1947).
80. H. Shechter, Record. Chem. Prog., 25, 55 (1964).
81. T. E. Stevens, J. Am. Chem. Soc., 81, 3593 (1959).

B29886